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(54) Title: COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

(57) Abstract

Compositions and methods for the therapy and diagnosis of cancer, such as breast cancer, are disclosed. Compositions may comprise one or more breast tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a breast tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as breast cancer. Diagnostic methods based on detecting a breast tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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WO 00/60076 PCT/US00/05308

COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

TECHNICAL FIELD

The present invention relates generally to compositions and methods for the treatment of breast cancer. The invention is more particularly related to polypeptides comprising at least a portion of a protein that is preferentially expressed in breast tumor tissue and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for treatment of breast cancer.

BACKGROUND OF THE INVENTION

Breast cancer is a significant health problem for women in the United States and throughout the world. Although advances have been made in detection and treatment of the disease, breast cancer remains the second leading cause of cancer-related deaths in women, affecting more than 180,000 women in the United States each year. For women in North America, the life-time odds of getting breast cancer are one in eight.

No vaccine or other universally successful method for the prevention or treatment of breast cancer is currently available. Management of the disease currently relies on a combination of early diagnosis (through routine breast screening procedures) and aggressive treatment, which may include one or more of a variety of treatments such as surgery, radiotherapy, chemotherapy and hormone therapy. The course of treatment for a particular breast cancer is often selected based on a variety of prognostic parameters, including an analysis of specific tumor markers. See, e.g., Porter-Jordan and Lippman, Breast Cancer 8:73-100 (1994). However, the use of established markers often leads to a result that is difficult to interpret, and the high mortality observed in breast cancer patients indicates that improvements are needed in the treatment, diagnosis and prevention of the disease.

Accordingly, there is a need in the art for improved methods for the treatment and diagnosis of breast cancer. The present invention fulfills these needs and further provides other related advantages.

SUMMARY OF THE INVENTION

The present invention provides compounds and methods for the treatment and diagnosis of cancer, such as breast cancer. In one aspect, isolated polypeptides are provided comprising at least a portion of a breast tumor protein or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with protein-specific antisera is not substantially diminished. With certain embodiments, the polypeptide comprises an amino acid sequence encoded by a polynucleotide selected from the group consisting of: (a) nucleotide sequences recited in SEQ ID NO: 1-61, 63-175, 178, 180, 182-313, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468; (b) complements of said nucleotide sequences; and (c) variants of a sequence of (a) or (b). In specific embodiments, the inventive polypeptides comprise at least a portion of a tumor antigen that comprises an amino acid sequence selected from the group consisting of SEQ ID NO: 62, 176, 179, 181 and 469-473.

In related aspects, isolated polynucleotides encoding the above polypeptides, or a portion thereof (such as a portion encoding at least 15 contiguous amino acid residues of a breast tumor protein), are provided. In specific embodiments, such polynucleotides comprise a sequence selected from the group consisting of sequences provided in SEQ ID NO: 1-61, 63-175, 178, 180, 182-313, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 and variants thereof The present invention further provides expression vectors comprising the above polynucleotides, together with host cells transformed or transfected with such expression vectors. In preferred embodiments, the host cells are selected from the group consisting of *E. coli*, yeast and mammalian cells.

In another aspect, the present invention provides fusion proteins comprising a first and a second inventive polypeptide or, alternatively, an inventive polypeptide and a known breast tumor antigen.

The present invention also provides pharmaceutical compositions comprising at least one of the above polypeptides, or a polynucleotide encoding such a polypeptide, and a physiologically acceptable carrier, together with vaccines. For prophylactic or therapeutic use, comprising at least one such polypeptide or polynucleotide in combination with an immunostimulant. Pharmaceutical compositions and vaccines comprising one or more of the above fusion proteins are also provided.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a breast tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) an immunostimulant.

In yet another aspect, methods are provided for inhibiting the development of breast cancer in a patient, comprising administering an effective amount of at least one of the above pharmaceutical compositions and/or vaccines.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a breast tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide;

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4⁺ and/or CD8⁺ T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a breast tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

The polypeptides disclosed herein may be usefully employed in the diagnosis and monitoring of breast cancer. In one aspect of the present invention, methods are provided for detecting a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; and (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in a patient. In preferred embodiments, the binding agent is an antibody, most preferably a monoclonal antibody. The cancer may be breast cancer.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that is capable of binding to one of the above polypeptides; (b) detecting in the sample an amount of a polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amounts of polypeptide detected in steps (b) and (c).

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Within related aspects, the present invention provides antibodies, preferably monoclonal antibodies, that bind to the inventive polypeptides, as well as diagnostic kits comprising such antibodies, and methods of using such antibodies to inhibit the development of breast cancer.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, diagnostic kits comprising the above oligonucleotide probes or primers are provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

BRIEF DESCRIPTION OF THE DRAWING AND SEQUENCE IDENTIFIERS

Fig. 1 shows the results of a Northern blot of the clone SYN18C6 (SEQ ID NO: 40).

SEQ ID NO: 1 is the determined cDNA sequence of JBT2.

SEQ ID NO: 2 is the determined cDNA sequence of JBT6.

SEQ ID NO: 3 is the determined cDNA sequence of JBT7.

SEQ ID NO: 4 is the determined cDNA sequence of JBT10. SEQ ID NO: 5 is the determined cDNA sequence of JBT13. SEQ ID NO: 6 is the determined cDNA sequence of JBT14. SEQ ID NO: 7 is the determined cDNA sequence of JBT15. SEQ ID NO: 8 is the determined cDNA sequence of JBT16. SEQ ID NO: 9 is the determined cDNA sequence of JBT17. SEQ ID NO: 10 is the determined cDNA sequence of JBT22. SEQ ID NO: 11 is the determined cDNA sequence of JBT25. SEQ ID NO: 12 is the determined cDNA sequence of JBT28. SEQ ID NO: 13 is the determined cDNA sequence of JBT32. SEQ ID NO: 14 is the determined cDNA sequence of JBT33. SEQ ID NO: 15 is the determined cDNA sequence of JBT34. SEQ ID NO: 16 is the determined cDNA sequence of JBT36. SEQ ID NO: 17 is the determined cDNA sequence of JBT37. SEQ ID NO: 18 is the determined cDNA sequence of JBT51. SEQ ID NO: 19 is the determined cDNA sequence of JBTT1. SEQ ID NO: 20 is the determined cDNA sequence of JBTT7. SEQ ID NO: 21 is the determined cDNA sequence of JBTT11. SEQ ID NO: 22 is the determined cDNA sequence of JBTT14. SEQ ID NO: 23 is the determined cDNA sequence of JBTT18. SEQ ID NO: 24 is the determined cDNA sequence of JBTT19. SEQ ID NO: 25 is the determined cDNA sequence of JBTT20. SEQ ID NO: 26 is the determined cDNA sequence of JBTT21. SEQ ID NO: 27 is the determined cDNA sequence of JBTT22. SEQ ID NO: 28 is the determined cDNA sequence of JBTT28. SEQ ID NO: 29 is the determined cDNA sequence of JBTT29. SEQ ID NO: 30 is the determined cDNA sequence of JBTT33. SEQ ID NO: 31 is the determined cDNA sequence of JBTT37. SEQ ID NO: 32 is the determined cDNA sequence of JBTT38. SEQ ID NO: 33 is the determined cDNA sequence of JBTT47. SEQ ID NO: 34 is the determined cDNA sequence of JBTT48.

SEQ ID NO: 35 is the determined cDNA sequence of JBTT50.

SEQ ID NO: 36 is the determined cDNA sequence of JBTT51.

SEQ ID NO: 37 is the determined cDNA sequence of JBTT52.

SEQ ID NO: 38 is the determined cDNA sequence of JBTT54.

SEQ ID NO: 39 is the determined cDNA sequence of SYN17F4.

SEQ ID NO: 40 is the determined cDNA sequence of SYN18C6.

SEQ ID NO: 41 is the determined cDNA sequence of SYN19A2.

SEQ ID NO: 42 is the determined cDNA sequence of SYN19C8.

SEQ ID NO: 43 is the determined cDNA sequence of SYN20A12.

SEQ ID NO: 44 is the determined cDNA sequence of SYN20G6.

SEQ ID NO: 45 is the determined cDNA sequence of SYN20G6-2.

SEQ ID NO: 46 is the determined cDNA sequence of SYN21B9.

SEQ ID NO: 47 is the determined cDNA sequence of SYN21B9-2.

SEQ ID NO: 48 is the determined cDNA sequence of SYN21C10.

SEQ ID NO: 49 is the determined cDNA sequence of SYN21G10.

SEQ ID NO: 50 is the determined cDNA sequence of SYN21G10-2.

SEQ ID NO: 51 is the determined cDNA sequence of SYN21G11.

SEQ ID NO: 52 is the determined cDNA sequence of SYN21G11-2.

SEQ ID NO: 53 is the determined cDNA sequence of SYN21H8.

SEQ ID NO: 54 is the determined cDNA sequence of SYN22A10.

SEQ ID NO: 55 is the determined cDNA sequence of SYN22A10-2.

SEQ ID NO: 56 is the determined cDNA sequence of SYN22A12.

SEQ ID NO: 57 is the determined cDNA sequence of SYN22A2.

SEQ ID NO: 58 is the determined cDNA sequence of SYN22B4.

SEQ ID NO: 59 is the determined cDNA sequence of SYN22C2.

SEQ ID NO: 60 is the determined cDNA sequence of SYN22E10.

SEQ ID NO: 61 is the determined cDNA sequence of SYN22F2.

SEQ ID NO: 62 is a predicted amino acid sequence for SYN18C6.

SEQ ID NO: 63 is the determined cDNA sequence of B723P.

SEQ ID NO: 64 is the determined cDNA sequence for B724P.

SEQ ID NO: 65 is the determined cDNA sequence of B770P.

SEQ ID NO: 66 is the determined cDNA sequence of B716P.

SEQ ID NO: 67 is the determined cDNA sequence of B725P.

SEQ ID NO: 68 is the determined cDNA sequence of B717P.

SEQ ID NO: 69 is the determined cDNA sequence of B771P.

SEQ ID NO: 70 is the determined cDNA sequence of B722P.

SEQ ID NO: 71 is the determined cDNA sequence of B726P.

SEQ ID NO: 72 is the determined cDNA sequence of B727P.

SEQ ID NO: 73 is the determined cDNA sequence of B728P.

SEQ ID NO: 74-87 are the determined cDNA sequences of isolated clones which show homology to known sequences.

SEQ ID NO: 88 is the determined cDNA sequence of 13053.

SEQ ID NO: 89 is the determined cDNA sequence of 13057.

SEQ ID NO: 90 is the determined cDNA sequence of 13059.

SEQ ID NO: 91 is the determined cDNA sequence of 13065.

SEQ ID NO: 92 is the determined cDNA sequence of 13067.

SEQ ID NO: 93 is the determined cDNA sequence of 13068.

SEQ ID NO: 94 is the determined cDNA sequence of 13071.

SEQ ID NO: 95 is the determined cDNA sequence of 13072.

SEQ ID NO: 96 is the determined cDNA sequence of 13073.

SEQ ID NO: 97 is the determined cDNA sequence of 13075.

SEQ ID NO: 98 is the determined cDNA sequence of 13078.

SEQ ID NO: 99 is the determined cDNA sequence of 13079.

SEQ ID NO: 100 is the determined cDNA sequence of 13081.

SEQ ID NO: 101 is the determined cDNA sequence of 13082.

SEQ ID NO: 102 is the determined cDNA sequence of 13092.

SEQ ID NO: 103 is the determined cDNA sequence of 13097.

SEQ ID NO: 104 is the determined cDNA sequence of 13101.

SEQ ID NO: 105 is the determined cDNA sequence of 13102.

SEQ ID NO: 106 is the determined cDNA sequence of 13119.

SEQ ID NO: 107 is the determined cDNA sequence of 13131.

SEQ ID NO: 108 is the determined cDNA sequence of 13133.

SEQ ID NO: 109 is the determined cDNA sequence of 13135. SEQ ID NO: 110 is the determined cDNA sequence of 13139. SEQ ID NO: 111 is the determined cDNA sequence of 13140. SEQ ID NO: 112 is the determined cDNA sequence of 13146. SEQ ID NO: 113 is the determined cDNA sequence of 13147. SEQ ID NO: 114 is the determined cDNA sequence of 13148. SEQ ID NO: 115 is the determined cDNA sequence of 13149. SEQ ID NO: 116 is the determined cDNA sequence of 13151. SEQ ID NO: 117 is the determined cDNA sequence of 13051 SEQ ID NO: 118 is the determined cDNA sequence of 13052 SEQ ID NO: 119 is the determined cDNA sequence of 13055 SEQ ID NO: 120 is the determined cDNA sequence of 13058 SEQ ID NO: 121 is the determined cDNA sequence of 13062 SEQ ID NO: 122 is the determined cDNA sequence of 13064 SEQ ID NO: 123 is the determined cDNA sequence of 13080 SEQ ID NO: 124 is the determined cDNA sequence of 13093 SEQ ID NO: 125 is the determined cDNA sequence of 13094 SEQ ID NO: 126 is the determined cDNA sequence of 13095 SEQ ID NO: 127 is the determined cDNA sequence of 13096 SEQ ID NO: 128 is the determined cDNA sequence of 13099 SEQ ID NO: 129 is the determined cDNA sequence of 13100 SEQ ID NO: 130 is the determined cDNA sequence of 13103 SEQ ID NO: 131 is the determined cDNA sequence of 13106 SEQ ID NO: 132 is the determined cDNA sequence of 13107 SEQ ID NO: 133 is the determined cDNA sequence of 13108 SEQ ID NO: 134 is the determined cDNA sequence of 13121 SEQ ID NO: 135 is the determined cDNA sequence of 13126 SEQ ID NO: 136 is the determined cDNA sequence of 13129 SEQ ID NO: 137 is the determined cDNA sequence of 13130 SEQ ID NO: 138 is the determined cDNA sequence of 13134 SEQ ID NO: 139 is the determined cDNA sequence of 13141

SEQ ID NO: 140 is the determined cDNA sequence of 13142 SEQ ID NO: 141 is the determined cDNA sequence of 14376 SEQ ID NO: 142 is the determined cDNA sequence of 14377 SEQ ID NO: 143 is the determined cDNA sequence of 14383 SEQ ID NO: 144 is the determined cDNA sequence of 14384 SEQ ID NO: 145 is the determined cDNA sequence of 14387 SEQ ID NO: 146 is the determined cDNA sequence of 14392 SEQ ID NO: 147 is the determined cDNA sequence of 14394 SEQ ID NO: 148 is the determined cDNA sequence of 14398 SEQ ID NO: 149 is the determined cDNA sequence of 14401 SEQ ID NO: 150 is the determined cDNA sequence of 14402 SEQ ID NO: 151 is the determined cDNA sequence of 14405 SEQ ID NO: 152 is the determined cDNA sequence of 14409 SEQ ID NO: 153 is the determined cDNA sequence of 14412 SEQ ID NO: 154 is the determined cDNA sequence of 14414 SEQ ID NO: 155 is the determined cDNA sequence of 14415 SEQ ID NO: 156 is the determined cDNA sequence of 14416 SEQ ID NO: 157 is the determined cDNA sequence of 14419 SEQ ID NO: 158 is the determined cDNA sequence of 14426 SEQ ID NO: 159 is the determined cDNA sequence of 14427 SEQ ID NO: 160 is the determined cDNA sequence of 14375 SEQ ID NO: 161 is the determined cDNA sequence of 14378 SEQ ID NO: 162 is the determined cDNA sequence of 14379 SEQ ID NO: 163 is the determined cDNA sequence of 14380 SEQ ID NO: 164 is the determined cDNA sequence of 14381 SEQ ID NO: 165 is the determined cDNA sequence of 14382 SEQ ID NO: 166 is the determined cDNA sequence of 14388 SEQ ID NO: 167 is the determined cDNA sequence of 14399 SEQ ID NO: 168 is the determined cDNA sequence of 14406 SEQ ID NO: 169 is the determined cDNA sequence of 14407 SEQ ID NO: 170 is the determined cDNA sequence of 14408

SEQ ID NO: 171 is the determined cDNA sequence of 14417

SEQ ID NO: 172 is the determined cDNA sequence of 14418

SEQ ID NO: 173 is the determined cDNA sequence of 14423

SEQ ID NO: 174 is the determined cDNA sequence of 14424

SEQ ID NO: 175 is the determined cDNA sequence of B726P-20

SEQ ID NO: 176 is the predicted amino acid sequence of B726P-20

SEQ ID NO: 177 is a PCR primer

SEQ ID NO: 178 is the determined cDNA sequence of B726P-74

SEQ ID NO: 179 is the predicted amino acid sequence of B726P-74

SEQ ID NO: 180 is the determined cDNA sequence of B726P-79

SEQ ID NO: 181 is the predicted amino acid sequence of B726P-79

SEQ ID NO: 182 is the determined cDNA sequence of 19439.1, showing homology to the mammaglobin gene

SEQ ID NO: 183 is the determined cDNA sequence of 19407.1, showing homology to the human keratin gene

SEQ ID NO: 184 is the determined cDNA sequence of 19428.1, showing homology to human chromosome 17 clone

SEQ ID NO: 185 is the determined cDNA sequence of B808P (19408), showing no significant homology to any known gene

SEQ ID NO: 186 is the determined cDNA sequence of 19460.1, showing no significant homology to any known gene

SEQ ID NO: 187 is the determined cDNA sequence of 19419.1, showing homology to Ig kappa light chain

SEQ ID NO: 188 is the determined cDNA sequence of 19411.1, showing homology to human alpha-1 collagen

SEQ ID NO: 189 is the determined cDNA sequence of 19420.1, showing homology to mus musculus proteinase-3

SEQ ID NO: 190 is the determined cDNA sequence of 19432.1, showing homology to human high motility group box

SEQ ID NO: 191 is the determined cDNA sequence of 19412.1, showing homology to the human plasminogen activator gene

SEQ ID NO: 192 is the determined cDNA sequence of 19415.1, showing homology to mitogen activated protein kinase

SEQ ID NO: 193 is the determined cDNA sequence of 19409.1, showing homology to the chondroitin sulfate proteoglycan protein

SEQ ID NO: 194 is the determined cDNA sequence of 19406.1, showing no significant homology to any known gene

SEQ ID NO: 195 is the determined cDNA sequence of 19421.1, showing homology to human fibronectin

SEQ ID NO: 196 is the determined cDNA sequence of 19426.1, showing homology to the retinoic acid receptor responder 3

SEQ ID NO: 197 is the determined cDNA sequence of 19425.1, showing homology to MyD88 mRNA

SEQ ID NO: 198 is the determined cDNA sequence of 19424.1, showing homology to peptide transporter (TAP-1) mRNA

SEQ ID NO: 199 is the determined cDNA sequence of 19429.1, showing no significant homology to any known gene

SEQ ID NO: 200 is the determined cDNA sequence of 19435.1, showing homology to human polymorphic epithelial mucin

SEQ ID NO: 201 is the determined cDNA sequence of B813P (19434.1), showing homology to human GATA-3 transcription factor

SEQ ID NO: 202 is the determined cDNA sequence of 19461.1, showing homology to the human AP-2 gene

SEQ ID NO: 203 is the determined cDNA sequence of 19450.1, showing homology to DNA binding regulatory factor

SEQ ID NO: 204 is the determined cDNA sequence of 19451.1, showing homology to Na/H exchange regulatory co-factor

SEQ ID NO: 205 is the determined cDNA sequence of 19462.1, showing no significant homology to any known gene

SEQ ID NO: 206 is the determined cDNA sequence of 19455.1, showing homology to human mRNA for histone HAS.Z

SEQ ID NO: 207 is the determined cDNA sequence of 19459.1, showing

homology to PAC clone 179N16

SEQ ID NO: 208 is the determined cDNA sequence of 19464.1, showing no significant homology to any known gene

SEQ ID NO: 209 is the determined cDNA sequence of 19414.1, showing homology to lipophilin B

SEQ ID NO: 210 is the determined cDNA sequence of 19413.1, showing homology to chromosome 17 clone hRPK.209_J_20

SEQ ID NO: 211 is the determined cDNA sequence of 19416.1, showing no significant homology to any known gene

SEQ ID NO: 212 is the determined cDNA sequence of 19437.1, showing homology to human clone 24976 mRNA

SEQ ID NO: 213 is the determined cDNA sequence of 19449.1, showing homology to mouse DNA for PG-M core protein

SEQ ID NO: 214 is the determined cDNA sequence of 19446.1, showing no significant homology to any known gene

SEQ ID NO: 215 is the determined cDNA sequence of 19452.1, showing no significant homology to any known gene

SEQ ID NO: 216 is the determined cDNA sequence of 19483.1, showing no significant homology to any known gene

SEQ ID NO: 217 is the determined cDNA sequence of 19526.1, showing homology to human lipophilin C

SEQ ID NO: 218 is the determined cDNA sequence of 19484.1, showing homology to the secreted cement gland protein XAG-2

SEQ ID NO: 219 is the determined cDNA sequence of 19470.1, showing no significant homology to any known gene

SEQ ID NO: 220 is the determined cDNA sequence of 19469.1, showing homology to the human HLA-DM gene

SEQ ID NO: 221 is the determined cDNA sequence of 19482.1, showing homology to the human pS2 protein gene

SEQ ID NO: 222 is the determined cDNA sequence of B805P (19468.1), showing no significant homology to any known gene

SEQ ID NO: 223 is the determined cDNA sequence of 19467.1, showing homology to human thrombospondin mRNA

SEQ ID NO: 224 is the determined cDNA sequence of 19498.1, showing homology to the CDC2 gene involved in cell cycle control

SEQ ID NO: 225 is the determined cDNA sequence of 19506.1, showing homology to human cDNA for TREB protein

SEQ ID NO: 226 is the determined cDNA sequence of B806P (19505.1), showing no significant homology to any known gene

SEQ ID NO: 227 is the determined cDNA sequence of 19486.1, showing homology to type I epidermal keratin

SEQ ID NO: 228 is the determined cDNA sequence of 19510.1, showing homology to glucose transporter for glycoprotein

SEQ ID NO: 229 is the determined cDNA sequence of 19512.1, showing homology to the human lysyl hydroxylase gene

SEQ ID NO: 230 is the determined cDNA sequence of 19511.1, showing homology to human palimotoyl-protein thioesterase

SEQ ID NO: 231 is the determined cDNA sequence of 19508.1, showing homology to human alpha enolase

SEQ ID NO: 232 is the determined cDNA sequence of B807P (19509.1), showing no significant homology to any known gene

SEQ ID NO: 233 is the determined cDNA sequence of B809P (19520.1), showing homology to clone 102D24 on chromosome 11q13.31

SEQ ID NO: 234 is the determined cDNA sequence of 19507.1, showing homology toprosome beta-subunit

SEQ ID NO: 235 is the determined cDNA sequence of 19525.1, showing homology to human pro-urokinase precursor

SEQ ID NO: 236 is the determined cDNA sequence of 19513.1, showing no significant homology to any known gene

SEQ ID NO: 237 is the determined cDNA sequence of 19517.1, showing homology to human PAC 128M19 clone

SEQ ID NO: 238 is the determined cDNA sequence of 19564.1, showing

homology to human cytochrome P450-IIB

SEQ ID NO: 239 is the determined cDNA sequence of 19553.1. showing homology to human GABA-A receptor pi subunit

SEQ ID NO: 240 is the determined cDNA sequence of B811P (19575.1), showing no significant homology to any known gene

SEQ ID NO: 241 is the determined cDNA sequence of B810P (19560.1), showing no significant homology to any known gene

SEQ ID NO: 242 is the determined cDNA sequence of 19588.1, showing homology to aortic carboxypetidase-like protein

SEQ ID NO: 243 is the determined cDNA sequence of 19551.1, showing homology to human BCL-1 gene

SEQ ID NO: 244 is the determined cDNA sequence of 19567.1, showing homology to human proteasome-related mRNA

SEQ ID NO: 245 is the determined cDNA sequence of B803P (19583.1), showing no significant homology to any known gene

SEQ ID NO: 246 is the determined cDNA sequence of B812P (19587.1), showing no significant homology to any known gene

SEQ ID NO: 247 is the determined cDNA sequence of B802P (19392.2), showing homology to human chromosome 17

SEQ ID NO: 248 is the determined cDNA sequence of 19393.2, showing homology to human nicein B2 chain

SEQ ID NO: 249 is the determined cDNA sequence of 19398.2, human MHC class II DQ alpha mRNA

SEQ ID NO: 250 is the determined cDNA sequence of B804P (19399.2), showing homology to human Xp22 BAC GSHB-184P14

SEQ ID NO: 251 is the determined cDNA sequence of 19401.2, showing homology to human ikB kinase-b gene

SEQ ID NO: 252 is the determined cDNA sequence of 20266, showing no significant homology to any known gene

SEQ ID NO: 253 is the determined cDNA sequence of B826P (20270), showing no significant homology to any known gene

SEQ ID NO: 254 is the determined cDNA sequence of 20274, showing no significant homology to any known gene

SEQ ID NO: 255 is the determined cDNA sequence of 20276, showing no significant homology to any known gene

SEQ ID NO: 256 is the determined cDNA sequence of 20277, showing no significant homology to any known gene

SEQ ID NO: 257 is the determined cDNA sequence of B823P (20280), showing no significant homology to any known gene

SEQ ID NO: 258 is the determined cDNA sequence of B821P (20281), showing no significant homology to any known gene

SEQ ID NO: 259 is the determined cDNA sequence of B824P (20294), showing no significant homology to any known gene

SEQ ID NO: 260 is the determined cDNA sequence of 20303, showing no significant homology to any known gene

SEQ ID NO: 261 is the determined cDNA sequence of B820P (20310), showing no significant homology to any known gene

SEQ ID NO: 262 is the determined cDNA sequence of B825P (20336), showing no significant homology to any known gene

SEQ ID NO: 263 is the determined cDNA sequence of B827P (20341), showing no significant homology to any known gene

SEQ ID NO: 264 is the determined cDNA sequence of 20941, showing no significant homology to any known gene

SEQ ID NO: 265 is the determined cDNA sequence of 20954, showing no significant homology to any known gene

SEQ ID NO: 266 is the determined cDNA sequence of 20961, showing no significant homology to any known gene

SEQ ID NO: 267 is the determined cDNA sequence of 20965, showing no significant homology to any known gene

SEQ ID NO: 268 is the determined cDNA sequence of 20975, showing no significant homology to any known gene

SEQ ID NO: 269 is the determined cDNA sequence of 20261, showing

homology to Human p120 catenin

SEQ ID NO: 270 is the determined cDNA sequence of B822P (20262), showing homology to Human membrane glycoprotein 4F2

SEQ ID NO: 271 is the determined cDNA sequence of 20265, showing homology to Human Na, K-ATPase Alpha 1

SEQ ID NO: 272 is the determined cDNA sequence of 20267, showing homology to Human heart HS 90, partial cds

SEQ ID NO: 273 is the determined cDNA sequence of 20268, showing homology to Human mRNA GPI-anchored protein p137

SEQ ID NO: 274 is the determined cDNA sequence of 20271, showing homology to Human cleavage stimulation factor 77 kDa subunit

SEQ ID NO: 275 is the determined cDNA sequence of 20272, showing homology to Human p190-B

SEQ ID NO: 276 is the determined cDNA sequence of 20273, showing homology to Human ribophorin

SEQ ID NO: 277 is the determined cDNA sequence of 20278, showing homology to Human ornithine amino transferase

SEQ ID NO: 278 is the determined cDNA sequence of 20279, showing homology to Human S-adenosylmethionine synthetase

SEQ ID NO: 279 is the determined cDNA sequence of 20293, showing homology to Human x inactivation transcript

SEQ ID NO: 280 is the determined cDNA sequence of 20300, showing homology to Human cytochrome p450

SEQ ID NO: 281 is the determined cDNA sequence of 20305, showing homology to Human elongation factor-1 alpha

SEQ ID NO: 282 is the determined cDNA sequence of 20306, showing homology to Human epithelial ets protein

SEQ ID NO: 283 is the determined cDNA sequence of 20307, showing homology to Human signal transducer mRNA

SEQ ID NO: 284 is the determined cDNA sequence of 20313, showing homology to Human GABA-A receptor pi subunit mRNA

SEQ ID NO: 285 is the determined cDNA sequence of 20317, showing homology to Human tyrosine phosphatase

SEQ ID NO: 286 is the determined cDNA sequence of 20318, showing homology to Human cathepsine B proteinase

SEQ ID NO: 287 is the determined cDNA sequence of 20320, showing homology to Human 2-phosphopyruvate-hydratase-alpha-enolase

SEQ ID NO: 288 is the determined cDNA sequence of 20321, showing homology to Human E-cadherin

SEQ ID NO: 289 is the determined cDNA sequence of 20322, showing homology to Human hsp86

SEQ ID NO: 290 is the determined cDNA sequence of B828P (20326), showing homology to Human x inactivation transcript

SEQ ID NO: 291 is the determined cDNA sequence of 20333, showing homology to Human chromatin regulator, SMARCA5

SEQ ID NO: 292 is the determined cDNA sequence of 20335, showing homology to Human sphingolipid activator protein 1

SEQ ID NO: 293 is the determined cDNA sequence of 20337, showing homology to Human hepatocyte growth factor activator inhibitor type 2

SEQ ID NO: 294 is the determined cDNA sequence of 20338, showing homology to Human cell ashesion molecule CD44

SEQ ID NO: 295 is the determined cDNA sequence of 20340, showing homology to Human nuclear factor (erythroid-derived)-like 1

SEQ ID NO: 296 is the determined cDNA sequence of 20938, showing homology to Human vinculin mRNA

SEQ ID NO: 297 is the determined cDNA sequence of 20939, showing homology to Human elongation factor EF-1-alpha

SEQ ID NO: 298 is the determined cDNA sequence of 20940, showing homology to Human nestin gene

SEQ ID NO: 299 is the determined cDNA sequence of 20942, showing homology to Human pancreatic ribonuclease

SEQ ID NO: 300 is the determined cDNA sequence of 20943, showing

homology to Human transcobalamin I

SEQ ID NO: 301 is the determined cDNA sequence of 20944, showing homology to Human beta-tubulin

SEQ ID NO: 302 is the determined cDNA sequence of 20946, showing homology to Human HS1 protein

SEQ ID NO: 303 is the determined cDNA sequence of 20947, showing homology to Human cathepsin B

SEQ ID NO: 304 is the determined cDNA sequence of 20948, showing homology to Human testis enhanced gene transcript

SEQ ID NO: 305 is the determined cDNA sequence of 20949, showing homology to Human elongation factor EF-1-alpha

SEQ ID NO: 306 is the determined cDNA sequence of 20950, showing homology to Human ADP-ribosylation factor 3

SEQ ID NO: 307 is the determined cDNA sequence of 20951, showing homology to Human IFP53 or WRS for tryptophanyl-tRNA synthetase

SEQ ID NO: 308 is the determined cDNA sequence of 20952, showing homology to Human cyclin-dependent protein kinase

SEQ ID NO: 308 is the determined cDNA sequence of 20957, showing homology to Human alpha-tubulin sioform 1

SEQ ID NO: 309 is the determined cDNA sequence of 20959, showing homology to Human tyrosine phosphatase-61bp deletion

SEQ ID NO: 310 is the determined cDNA sequence of 20966, showing homology to Human tyrosine phosphatase

SEQ ID NO: 311 is the determined cDNA sequence of B830P (20976), showing homology to Human nuclear factor NF 45

SEQ ID NO: 312 is the determined cDNA sequence of B829P (20977), showing homology to Human delta-6 fatty acid desaturase

SEQ ID NO: 313 is the determined cDNA sequence of 20978, showing homology to Human nuclear aconitase

SEQ ID NO: 314 is the determined cDNA sequence of 19465, showing no significant homology to any known gene.

SEQ ID NO: 315 is the determined cDNA sequence of clone 23176. SEQ ID NO: 316 is the determined cDNA sequence of clone 23140. SEQ ID NO: 317 is the determined cDNA sequence of clone 23166. SEQ ID NO: 318 is the determined cDNA sequence of clone 23167. SEQ ID NO: 319 is the determined cDNA sequence of clone 23177. SEQ ID NO: 320 is the determined cDNA sequence of clone 23217. SEQ ID NO: 321 is the determined cDNA sequence of clone 23169. SEQ ID NO: 322 is the determined cDNA sequence of clone 23160. SEQ ID NO: 323 is the determined cDNA sequence of clone 23182. SEQ ID NO: 324 is the determined cDNA sequence of clone 23232. SEQ ID NO: 325 is the determined cDNA sequence of clone 23203. SEQ ID NO: 326 is the determined cDNA sequence of clone 23198. SEQ ID NO: 327 is the determined cDNA sequence of clone 23224. SEQ ID NO: 328 is the determined cDNA sequence of clone 23142. SEQ ID NO: 329 is the determined cDNA sequence of clone 23138. SEQ ID NO: 330 is the determined cDNA sequence of clone 23147. SEQ ID NO: 331 is the determined cDNA sequence of clone 23148. SEQ ID NO: 332 is the determined cDNA sequence of clone 23149. SEQ ID NO: 333 is the determined cDNA sequence of clone 23172. SEQ ID NO: 334 is the determined cDNA sequence of clone 23158. SEQ ID NO: 335 is the determined cDNA sequence of clone 23156. SEQ ID NO: 336 is the determined cDNA sequence of clone 23221. SEQ ID NO: 337 is the determined cDNA sequence of clone 23223. SEQ ID NO: 338 is the determined cDNA sequence of clone 23155. SEQ ID NO: 339 is the determined cDNA sequence of clone 23225. SEQ ID NO: 340 is the determined cDNA sequence of clone 23226. SEQ ID NO: 341 is the determined cDNA sequence of clone 23228. SEQ ID NO: 342 is the determined cDNA sequence of clone 23229. SEQ ID NO: 343 is the determined cDNA sequence of clone 23231. SEQ ID NO: 344 is the determined cDNA sequence of clone 23154. SEQ ID NO: 345 is the determined cDNA sequence of clone 23157.

SEQ ID NO: 346 is the determined cDNA sequence of clone 23153. SEQ ID NO: 347 is the determined cDNA sequence of clone 23159. SEQ ID NO: 348 is the determined cDNA sequence of clone 23152. SEQ ID NO: 349 is the determined cDNA sequence of clone 23161. SEQ ID NO: 350 is the determined cDNA sequence of clone 23162. SEQ ID NO: 351 is the determined cDNA sequence of clone 23163. SEQ ID NO: 352 is the determined cDNA sequence of clone 23164. SEQ ID NO: 353 is the determined cDNA sequence of clone 23165. SEQ ID NO: 354 is the determined cDNA sequence of clone 23151. SEQ ID NO: 355 is the determined cDNA sequence of clone 23150. SEQ ID NO: 356 is the determined cDNA sequence of clone 23168. SEQ ID NO: 357 is the determined cDNA sequence of clone 23146. SEQ ID NO: 358 is the determined cDNA sequence of clone 23170. SEQ ID NO: 359 is the determined cDNA sequence of clone 23171. SEQ ID NO: 360 is the determined cDNA sequence of clone 23145. SEQ ID NO: 361 is the determined cDNA sequence of clone 23174. SEQ ID NO: 362 is the determined cDNA sequence of clone 23175. SEQ ID NO: 363 is the determined cDNA sequence of clone 23144. SEQ ID NO: 364 is the determined cDNA sequence of clone 23178. SEQ ID NO: 365 is the determined cDNA sequence of clone 23179. SEO ID NO: 366 is the determined cDNA sequence of clone 23180. SEQ ID NO: 367 is the determined cDNA sequence of clone 23181. SEQ ID NO: 368 is the determined cDNA sequence of clone 23143 SEQ ID NO: 369 is the determined cDNA sequence of clone 23183. SEQ ID NO: 370 is the determined cDNA sequence of clone 23184. SEQ ID NO: 371 is the determined cDNA sequence of clone 23185. SEQ ID NO: 372 is the determined cDNA sequence of clone 23186. SEQ ID NO: 373 is the determined cDNA sequence of clone 23187. SEQ ID NO: 374 is the determined cDNA sequence of clone 23190. SEQ ID NO: 375 is the determined cDNA sequence of clone 23189. SEQ ID NO: 376 is the determined cDNA sequence of clone 23202.

SEQ ID NO: 378 is the determined cDNA sequence of clone 23191. SEQ ID NO: 379 is the determined cDNA sequence of clone 23188. SEQ ID NO: 380 is the determined cDNA sequence of clone 23194. SEQ ID NO: 381 is the determined cDNA sequence of clone 23196. SEQ ID NO: 382 is the determined cDNA sequence of clone 23195. SEQ ID NO: 383 is the determined cDNA sequence of clone 23193. SEQ ID NO: 384 is the determined cDNA sequence of clone 23199. SEQ ID NO: 385 is the determined cDNA sequence of clone 23200. SEQ ID NO: 386 is the determined cDNA sequence of clone 23192. SEQ ID NO: 387 is the determined cDNA sequence of clone 23201. SEQ ID NO: 388 is the determined cDNA sequence of clone 23141. SEQ ID NO: 389 is the determined cDNA sequence of clone 23139. SEQ ID NO: 390 is the determined cDNA sequence of clone 23204. SEQ ID NO: 391 is the determined cDNA sequence of clone 23205. SEQ ID NO: 392 is the determined cDNA sequence of clone 23206. SEQ ID NO: 393 is the determined cDNA sequence of clone 23207. SEQ ID NO: 394 is the determined cDNA sequence of clone 23208. SEQ ID NO: 395 is the determined cDNA sequence of clone 23209. SEQ ID NO: 396 is the determined cDNA sequence of clone 23210. SEQ ID NO: 397 is the determined cDNA sequence of clone 23211. SEQ ID NO: 398 is the determined cDNA sequence of clone 23212. SEQ ID NO: 399 is the determined cDNA sequence of clone 23214. SEQ ID NO: 400 is the determined cDNA sequence of clone 23215. SEQ ID NO: 401 is the determined cDNA sequence of clone 23216. SEQ ID NO: 402 is the determined cDNA sequence of clone 23137. SEQ ID NO: 403 is the determined cDNA sequence of clone 23218. SEQ ID NO: 404 is the determined cDNA sequence of clone 23220. SEQ ID NO: 405 is the determined cDNA sequence of clone 19462. SEQ ID NO: 406 is the determined cDNA sequence of clone 19430. SEQ ID NO: 407 is the determined cDNA sequence of clone 19407. SEQ ID NO: 408 is the determined cDNA sequence of clone 19448.

SEQ ID NO: 409 is the determined cDNA sequence of clone 19447.

SEQ ID NO: 410 is the determined cDNA sequence of clone 19426.

SEQ ID NO: 411 is the determined cDNA sequence of clone 19441.

SEQ ID NO: 412 is the determined cDNA sequence of clone 19454.

SEQ ID NO: 413 is the determined cDNA sequence of clone 19463.

SEQ ID NO: 414 is the determined cDNA sequence of clone 19419.

SEQ ID NO: 415 is the determined cDNA sequence of clone 19434.

SEQ ID NO: 416 is the determined extended cDNA sequence of B820P.

SEQ ID NO: 417 is the determined extended cDNA sequence of B821P.

SEQ ID NO: 418 is the determined extended cDNA sequence of B822P.

SEQ ID NO: 419 is the determined extended cDNA sequence of B823P.

SEQ ID NO: 420 is the determined extended cDNA sequence of B824P.

SEQ ID NO: 421 is the determined extended cDNA sequence of B825P.

SEQ ID NO: 422 is the determined extended cDNA sequence of B826P.

SEQ ID NO: 423 is the determined extended cDNA sequence of B827P.

SEQ ID NO: 424 is the determined extended cDNA sequence of B828P.

SEQ ID NO: 425 is the determined extended cDNA sequence of B829P.

SEQ ID NO: 426 is the determined extended cDNA sequence of B830P.

SEQ ID NO: 427 is the determined cDNA sequence of clone 266B4.

SEQ ID NO: 428 is the determined cDNA sequence of clone 22892.

SEQ ID NO: 429 is the determined cDNA sequence of clone 266G3.

SEQ ID NO: 430 is the determined cDNA sequence of clone 22890.

SEQ ID NO: 431 is the determined cDNA sequence of clone 264B4.

SEQ ID NO: 432 is the determined cDNA sequence of clone 22883.

SEQ ID NO: 433 is the determined cDNA sequence of clone 22882.

SEQ ID NO: 434 is the determined cDNA sequence of clone 22880.

SEQ ID NO: 435 is the determined cDNA sequence of clone 263G1.

SEQ ID NO: 436 is the determined cDNA sequence of clone 263G6.

SEQ ID NO: 437 is the determined cDNA sequence of clone 262B2.

SEQ ID NO: 438 is the determined cDNA sequence of clone 262B6.

SEQ ID NO: 439 is the determined cDNA sequence of clone 22869.

SEQ ID NO: 440 is the determined cDNA sequence of clone 21374.

SEQ ID NO: 441 is the determined cDNA sequence of clone 21362.

SEQ ID NO: 442 is the determined cDNA sequence of clone 21349.

SEQ ID NO: 443 is the determined cDNA sequence of clone 21309.

SEQ ID NO: 444 is the determined cDNA sequence of clone 21097.

SEQ ID NO: 445 is the determined cDNA sequence of clone 21096.

SEQ ID NO: 446 is the determined cDNA sequence of clone 21094.

SEQ ID NO: 447 is the determined cDNA sequence of clone 21093.

SEQ ID NO: 448 is the determined cDNA sequence of clone 21091.

SEQ ID NO: 449 is the determined cDNA sequence of clone 21089.

SEQ ID NO: 450 is the determined cDNA sequence of clone 21087.

SEQ ID NO: 451 is the determined cDNA sequence of clone 21085.

SEQ ID NO: 452 is the determined cDNA sequence of clone 21084.

SEQ ID NO: 453 is a first partial cDNA sequence of clone 2BT1-40.

SEQ ID NO: 454 is a second partial cDNA sequence of clone 2BT1-40.

SEQ ID NO: 455 is the determined cDNA sequence of clone 21063.

SEQ ID NO: 456 is the determined cDNA sequence of clone 21062.

SEO ID NO: 457 is the determined cDNA sequence of clone 21060.

SEQ ID NO: 458 is the determined cDNA sequence of clone 21053.

SEO ID NO: 459 is the determined cDNA sequence of clone 21050.

SEQ ID NO: 460 is the determined cDNA sequence of clone 21036.

SEQ ID NO: 461 is the determined cDNA sequence of clone 21037.

SEQ ID NO: 462 is the determined cDNA sequence of clone 21048.

SEQ ID NO: 463 is a consensus DNA sequence of B726P (referred to as B726P-spliced seq B726P).

SEQ ID NO: 464 is the determined cDNA sequence of a second splice form of B726P (referred to as 27490.seq B726P).

SEQ ID NO: 465 is the determined cDNA sequence of a third splice form of B726P (referred to as 27068.seq_B726P).

SEQ ID NO: 466 is the determined cDNA sequence of a second splice form of B726P (referred to as 23113.seq_B726P).

SEQ ID NO: 467 is the determined cDNA sequence of a second splice form of B726P (referred to as 23103.seq B726P).

SEQ ID NO: 468 is the determined cDNA sequence of a second splice form of B726P (referred to as 19310.seq B726P).

SEQ ID NO: 469 is the predicted amino acid sequence encoded by the upstream ORF of SEQ ID NO: 463.

SEQ ID NO: 470 is the predicted amino acid sequence encoded by SEQ ID NO: 464.

SEQ ID NO: 471 is the predicted amino acid sequence encoded by SEQ ID NO: 465.

SEQ ID NO: 472 is the predicted amino acid sequence encoded by SEQ ID NO: 466.

SEQ ID NO: 473 is the predicted amino acid sequence encoded by SEQ ID NO: 467.

DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as breast cancer. The compositions described herein may include breast tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a breast tumor protein or a variant thereof. A "breast tumor protein" is a protein that is expressed in breast tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain breast tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with breast cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of

binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human breast tumor proteins. Sequences of polynucleotides encoding specific tumor proteins are provided in SEQ ID NOS:1-175, 178, 180 and 182-468.

BREAST TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a breast tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a breast tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a breast tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a breast tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide

sequence that encodes a native breast tumor protein or a portion thereof. The term "variants" also encompasses homologous genes of xenogenic origin.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions, usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 Methods in Enzymology vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) CABIOS 5:151-153; Myers, E.W. and Muller W. (1988) CABIOS 4:11-17; Robinson, E.D. (1971) Comb. Theor 11:105; Santou, N. Nes, M. (1987) Mol. Biol. Evol. 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) Proc. Natl. Acad., Sci. USA 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (i.e. gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two

sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (i.e. the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native breast tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a breast tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially

as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as breast tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a breast tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with ³²P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed

using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known region. A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence. Full length DNA sequences may also be obtained by analysis of genomic fragments.

Certain nucleic acid sequences of cDNA molecules encoding portions of breast tumor proteins are provided in SEQ ID NO: 1-175, 178, 180 and 182-468. The

isolation of these sequences is described in detail below.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a breast tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a breast tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (i.e., an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (see Gee et al., In Huber and Carr, Molecular and Immunologic Approaches, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (e.g., promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and

still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability in vivo. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl-, methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). The polynucleotides may also be administered as naked plasmid vectors. Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

BREAST TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a breast tumor protein or a variant thereof, as described herein. As noted above, a "breast tumor protein" is a protein that is expressed by breast tumor cells. Proteins that are breast tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with breast cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is

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recognized (i.e., specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a breast tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (e.g., 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, Fundamental Immunology, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera and/or Tcell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (i.e., they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native breast tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (e.g., in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using. for example, ¹²⁵I-labeled Protein A.

As noted above, a composition may comprise a variant of a native breast tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native breast tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigen-specific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein.

Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. A "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, higher eukaryotic and plant cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at

least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al.,

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Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986).

LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (see Biotechnology 10:795-798, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

BINDING AGENTS

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a breast tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a breast tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a breast tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10³ L/mol. The binding constant may be

determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as breast cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a breast tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically.

Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane,

Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include ⁹⁰Y, ¹²³I, ¹²⁵I, ¹³¹I, ¹⁸⁶Re, ¹⁸⁸Re, ²¹¹At, and ²¹²Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diphtheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and

immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a breast tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the ISOLEXTM system, available from Nexell Therapeutics Inc., Irvine, CA (see also U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a breast tumor polypeptide, polynucleotide encoding a breast tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a breast tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a breast tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively, detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased

rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a breast tumor polypeptide (100 ng/ml - 100 μg/ml, preferably 200 ng/ml - 25 μg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a breast tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4⁺ and/or CD8⁺. Breast tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4⁺ or CD8⁺ T cells that proliferate in response to a breast tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a breast tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a breast tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a breast tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions or immunogenic compositions (i.e., vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and an immunostimulant. An immunostimulant

may be any substance that enhances an immune response to an exogenous antigen. Examples of immunostimulants include adjuvants, biodegradable microspheres (e.g., polylactic galactide) and liposomes (into which the compound is incorporated; see e.g., Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner et al., Vaccine 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, Biotechniques 6:616-627, 1988; Rosenfeld et al., Science 252:431-434, 1991; Kolls et al., Proc. Natl. Acad. Sci. USA 91:215-219, 1994; Kass-Eisler et al., Proc. Natl. Acad. Sci. USA 90:11498-11502, 1993; Guzman et al., Circulation 88:2838-2848, 1993; and Guzman et al., Cir. Res. 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., Science 259:1745-1749, 1993 and reviewed by Cohen, Science 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of immunostimulants may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants

are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable microspheres; monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, TNF-α, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6 and IL-10) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt. MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT) (see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153,

or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule, sponge or gel (composed of polysaccharides, for example) that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects per se and/or to be immunologically compatible with the receiver (i.e., matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells

or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*), their ability to take up, process and present antigens with high efficiency, and their ability to activate naïve T cell responses. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNFα, CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce differentiation, maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor and mannose receptor. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell

surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80, CD86 and 4-1BB).

APCs may generally be transfected with a polynucleotide encoding a breast tumor protein (or portion or other variant thereof) such that the breast tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the breast tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

CANCER THERAPY

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as breast cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or

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following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune responsemodifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth *in vitro*, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition *in vivo* are well known in the art. Such *in vitro* culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example,

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antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term *in vivo*. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous, intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccine-dependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to non-vaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of

host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a breast tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more breast tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as breast cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a breast tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length breast tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about 10 μ g, and preferably about 100 ng to about 1 μ g, is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with breast cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined

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by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20TM. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence of absence of a cancer, such as breast cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond

to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use breast tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such breast tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a breast tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4⁺ and/or CD8⁺ T cells isolated from a patient is incubated with a breast tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with polypeptide (e.g., 5 - 25 μg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of breast tumor polypeptide to serve as a control. For CD4⁺ T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a breast tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a breast tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the breast tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a breast tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%, preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a breast tumor protein that is at least 10 nucleotides,

and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NOS:1-175, 178, 180 and 182-468. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain in vivo diagnostic assays may be performed directly on a tumor.

One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple breast tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a breast tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a breast tumor protein in a biological sample. Such kits generally comprise at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a breast tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a breast tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

EXAMPLES

Example 1

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES

This Example describes the isolation of breast tumor polypeptides from a breast tumor cDNA library.

A cDNA subtraction library containing cDNA from breast tumor subtracted with normal breast cDNA was constructed as follows. Total RNA was extracted from primary tissues using Trizol reagent (Gibco BRL Life Technologies, Gaithersburg, MD) as described by the manufacturer. The polyA+ RNA was purified using an oligo(dT) cellulose column according to standard protocols. First strand cDNA was synthesized using the primer supplied in a Clontech PCR-Select cDNA Subtraction Kit (Clontech, Palo Alto, CA). The driver DNA consisted of cDNAs from two normal breast tissues with the tester cDNA being from three primary breast tumors. Doublestranded cDNA was synthesized for both tester and driver, and digested with a combination of endonucleases (MluI, MscI, PvuII, SalI and StuI) which recognize six base pairs DNA. This modification increased the average cDNA size dramatically compared with cDNAs generated according to the protocol of Clontech (Palo Alto, CA). The digested tester cDNAs were ligated to two different adaptors and the subtraction was performed according to Clontech's protocol. The subtracted cDNAs were subjected to two rounds of PCR amplification, following the manufacturer's protocol. The resulting PCR products were subcloned into the TA cloning vector, pCRII (Invitrogen, San Diego, CA) and transformed into ElectroMax E. coli DH10B cells (Gibco BRL Life, Technologies) by electroporation. DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division (Foster City, CA) Automated Sequencer Model 373A.

Sixty-three distinct cDNA clones were found in the subtracted breast tumor-specific cDNA library. The determined one strand (5' or 3') cDNA sequences for the clones are provided in SEQ ID NO: 1-61, 72 and 73, respectively. Comparison of these cDNA sequences with known sequences in the gene bank using the EMBL and GenBank databases (Release 97) revealed no significant homologies to the sequences provided in SEQ ID NO: 14, 21, 22, 27, 29, 30, 32, 38, 44, 45, 53, 72 and 73. The sequences of SEQ ID NO: 1, 3, 16, 17, 34, 48, 57, 60 and 61 were found to represent known human genes. The sequences of SEQ ID NO: 2, 4, 23, 39 and 50 were found to show some similarity to previously identified non-human genes. The remaining clones (SEQ ID NO: 5-13, 15, 18-20, 24-26, 28, 31, 33, 35-37, 40-43, 46, 47, 49, 51, 52, 54-56, 58 and 59) were found to show at least some degree of homology to previously identified expressed sequence tags (ESTs).

To determine mRNA expression levels of the isolated cDNA clones, cDNA clones from the breast subtraction described above were randomly picked and colony PCR amplified. Their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were arrayed onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. The microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. Data was analyzed using Synteni provided GEMTOOLS Software. Of the seventeen cDNA clones examined, those of SEQ ID NO: 40, 46, 59 and 73 were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, PBMC, colon, fetal tissue, salivary gland, bone marrow, lung, pancreas, large intestine, spinal cord, adrenal gland, kidney, pancreas, liver, stomach, skeletal muscle, heart, small intestine, skin, brain and human mammary epithelial cells). The clones of SEQ ID NO: 41 and 48 were found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested, with the exception of bone marrow. The clone of SEQ ID NO: 42 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested except bone marrow and spinal cord. The clone of SEQ ID NO: 43 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord, heart and small intestine. The clone of SEQ ID NO: 51 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large intestine. The clone of SEQ ID NO: 54 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of PBMC, stomach and small intestine. The clone of SEQ ID NO: 56 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of large and small intestine, human mammary epithelia cells and SCID mouse-passaged breast tumor. The clone of SEQ ID NO: 60 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of spinal cord and heart. The clone of SEQ ID NO: 61 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of small intestine. The clone of SEQ ID NO: 72 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of small intestine. The clone of SEQ ID NO: 72 was found to be over-expressed in breast tumor and expressed at low levels in all other tissues tested with the exception of colon and salivary gland.

The results of a Northern blot analysis of the clone SYN18C6 (SEQ ID NO: 40) are shown in Fig. 1. A predicted protein sequence encoded by SYN18C6 is provided in SEQ ID NO: 62.

Additional cDNA clones that are over-expressed in breast tumor tissue were isolated from breast cDNA subtraction libraries as follows. Breast subtraction libraries were prepared, as described above, by PCR-based subtraction employing pools of breast tumor cDNA as the tester and pools of either normal breast cDNA or cDNA from other normal tissues as the driver. cDNA clones from breast subtraction were randomly picked and colony PCR amplified and their mRNA expression levels in breast tumor, normal breast and various other normal tissues were determined using the microarray technology described above. Twenty-four distinct cDNA clones were found to be over-expressed in breast tumor and expressed at low levels in all normal tissues tested (breast, brain, liver, pancreas, lung, salivary gland, stomach, colon, kidney, bone marrow, skeletal muscle, PBMC, heart, small intestine, adrenal gland, spinal cord, large intestine and skin). The determined partial cDNA sequences for these clones are provided in SEQ ID NO: 63-87. Comparison of the sequences of SEQ ID NO: 74-87

with those in the gene bank as described above, revealed homology to previously identified human genes. No significant homologies were found to the sequences of SEQ ID NO: 63-73.

Three DNA isoforms for the clone B726P (partial sequence provided in SEQ ID NO: 71) were isolated as follows. A radioactive probe was synthesized from B726P by excising B726P DNA from a pT7Blue vector (Novagen) by a BamHI/XbaI restriction digest and using the resulting DNA as the template in a single-stranded PCR in the presence of $[\alpha$ -32P]dCTP. The sequence of the primer employed for this PCR is provided in SEQ ID NO: 177. The resulting radioactive probe was used to probe a directional cDNA library and a random-primed cDNA library made using RNA isolated from breast tumors. Eighty-five clones were identified, excised, purified and sequenced. Of these 85 clones, three were found to each contain a significant open reading frame. The determined cDNA sequence of the isoform B726P-20 is provided in SEQ ID NO: 175, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 176. The determined cDNA sequence of the isoform B726P-74 is provided in SEQ ID NO: 178, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 179. The determined cDNA sequence of the isoform B726P-79 is provided in SEQ ID NO: 180, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 181.

Efforts to obtain a full-length clone of B726P using standard techniques led to the isolation of five additional clones that represent additional 5' sequence of B726P. These clones appear to be alternative splice forms of the same gene. The determined cDNA sequences of these clones are provided in SEQ ID NO: 464-468, with the predicted amino acid sequences encoded by SEQ ID NO: 464-467 being provided in SEQ ID NO: 470-473, respectively. Using standard computer techniques, a 3,681 bp consensus DNA sequence (SEQ ID NO: 463) was created that contains two large open reading frames. The downstream ORF encodes the predicted amino acid sequence of SEQ ID NO: 181. The predicted amino acid sequence encoded by the upstream ORF is provided in SEQ ID NO: 469.

Further isolation of individual clones that are over-expressed in breast tumor tissue was conducted using cDNA subtraction library techniques described above. In particular, a cDNA subtraction library containing cDNA from breast tumors subtracted with five other normal human tissue cDNAs (brain, liver, PBMC, pancreas and normal breast) was utilized in this screening. From the original subtraction, one hundred seventy seven clones were selected to be further characterized by DNA sequencing and microarray analysis. Microarray analysis demonstrated that the sequences in SEQ ID NO: 182-251 were 2 or more fold over-expressed in human breast tumor tissues over normal human tissues. No significant homologies were found for nineteen of these clones, including, SEQ ID NO: 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245 and 246, with the exception of some previously identified expressed sequence tags (ESTs). The remaining clones share some homology to previously identified genes, specifically SEQ ID NO: 181-184, 187-193, 195-198, 200-204, 206, 207, 209, 210, 212, 213, 217, 218, 220, 221, 223-225, 227-231, 233-235, 237-239, 242-244 and 247-251.

Of the seventy clones showing over-expression in breast tumor tissues, fifteen demonstrated particularly good expression levels in breast tumor over normal human tissues. The following eleven clones did not show any significant homology to any known genes. Clone 19463.1 (SEQ ID NO: 185) was over-expressed in the majority of breast tumors and also in the SCID breast tumors tested (refer to Example 2); additionally, over-expression was found in a majority of normal breast tissues. Clone 19483.1 (SEQ ID NO: 216) was over-expressed in a few breast tumors, with no overexpression in any normal tissues tested. Clone 19470.1 (SEQ ID NO: 219) was found to be slightly over-expressed in some breast tumors. Clone 19468.1 (SEQ ID NO: 222) was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19505.1 (SEQ ID NO: 226) was found to be slightly over-expressed in 50% of breast tumors, as well as in SCID tumor tissues, with some degree of over-expression in found in normal breast. Clone 1509.1 (SEQ ID NO: 232) was found to be over-expressed in very few breast tumors, but with a certain degree of over-expression in metastatic breast tumor tissues, as well as no significant over-expression found in normal tissues. Clone 19513.1 (SEQ ID NO: 236) was shown to be slightly over-expressed in few breast

tumors, with no significant over-expression levels found in normal tissues. Clone 19575.1 (SEQ ID NO: 240) showed low level over-expression in some breast tumors and also in normal breast. Clone 19560.1 (SEQ ID NO: 241) was over-expressed in 50% of breast tumors tested, as well as in some normal breast tissues. Clone 19583.1 (SEQ ID NO: 245) was slightly over-expressed in some breast tumors, with very low levels of over-expression found in normal tissues. Clone 19587.1 (SEQ ID NO: 246) showed low level over-expression in some breast tumors and no significant over-expression in normal tissues.

Clone 19520.1 (SEQ ID NO: 233), showing homology to clone 102D24 on chromosome 11q13.31, was found to be over-expressed in breast tumors and in SCID tumors. Clone 19517.1 (SEQ ID NO: 237), showing homology to human PAC 128M19 clone, was found to be slightly over-expressed in the majority of breast tumors tested. Clone 19392.2 (SEQ ID NO: 247), showing homology to human chromosome 17, was shown to be over-expressed in 50% of breast tumors tested. Clone 19399.2 (SEQ ID NO: 250), showing homology to human Xp22 BAC GSHB-184P14, was shown to be slightly over-expressed in a limited number of breast tumors tested.

In subsequent studies, 64 individual clones were isolated from a subtracted cDNA library containing cDNA from a pool of breast tumors subtracted with cDNA from five normal tissues (brain, liver, PBMC, pancreas and normal breast). The subtracted cDNA library was prepared as described above with the following modification. A combination of five six-base cutters (MluI, MscI, PvuII, Sa1I and StuI) was used to digest the cDNA instead of RsaI. This resulted in an increase in the average insert size from 300 bp to 600 bp. The 64 isolated clones were colony PCR amplified and their mRNA expression levels in breast tumor tissue, normal breast and various other normal tissues were examined by microarray technology as described above. The determined cDNA sequences of 11 clones which were found to be over-expressed in breast tumor tissue are provided in SEQ ID NO: 405-415. Comparison of these sequences to those in the public database, as outlined above, revealed homologies between the sequences of SEQ ID NO: 408, 411, 413 and 414 and previously isolated ESTs. The sequences of SEQ ID NO: 405-407, 409, 410, 412 and 415 were found to show some homology to previously identified sequences.

In further studies, a subtracted cDNA library was prepared from cDNA from metastatic breast tumors subtracted with a pool of cDNA from five normal tissues (breast, brain, lung, pancreas and PBMC) using the PCR-subtraction protocol of Clontech, described above. The determined cDNA sequences of 90 clones isolated from this library are provided in SEQ ID NO: 315-404. Comparison of these sequences with those in the public database, as described above, revealed no significant homologies to the sequence of SEQ ID NO: 366. The sequences of SEQ ID NO: 320-324, 342, 353, 367, 368, 377, 382, 385, 389, 395, 397 and 400 were found to show some homology to previously isolated ESTs. The remaining sequences were found to show homology to previously identified gene sequences.

In yet further studies, a subtracted cDNA library (referred to as 2BT) was prepared from cDNA from breast tumors subtracted with a pool of cDNA from six normal tissues (liver, brain, stomach, small intestine, kidney and heart) using the PCRsubtraction protocol of Clontech, described above. cDNA clones isolated from this subtraction were subjected to DNA microarray analysis as described above and the resulting data subjected to four modified Gemtools analyses. The first analysis compared 28 breast tumors with 28 non-breast normal tissues. A mean over-expression of at least 2.1 fold was used as a selection cut-off. The second analysis compared 6 metastatic breast tumors with 29 non-breast normal tissues. A mean over-expression of at least 2.5 fold was used as a cut-off. The third and fourth analyses compared 2 early SCID mousepassaged with 2 late SCID mouse-passaged tumors. A mean over-expression in the early or late passaged tumors of 2.0 fold or greater was used as a cut-off. In addition, a visual analysis was performed on the microarray data for the 2BT clones. The determined cDNA sequences of 13 clones identified in the visual analysis are provided in SEQ ID NO: 427-439. The determined cDNA sequences of 22 clones identified using the modified Gemtools analysis are provided in SEQ ID NO: 440-462, wherein SEQ ID NO: 453 and 454 represent two partial, non-overlapping, sequences of the same clone.

Comparison of the clone sequences of SEQ ID NO: 436 and 437 (referred to as 263G6 and 262B2) with those in the public databases, as described above, revealed no significant homologies to previously identified sequences. The sequences of SEQ ID NO: 427, 429, 431, 435, 438, 441, 443, 444, 445, 446, 450, 453 and 454 (referred to as

266B4, 266G3, 264B4, 263G1, 262B6, 2BT2-34, 2BT1-77, 2BT1-62, 2BT1-60,61, 2BT1-59, 2BT1-52 and 2BT1-40, respectively) showed some homology to previously isolated expressed sequences tags (ESTs). The sequences of SEQ ID NO: 428, 430, 432, 433, 434, 439, 440, 442, 447, 448, 449, 451, 452 and 455-462 (referred to as clones 22892, 22890, 22883, 22882, 22880, 22869, 21374, 21349, 21093, 21091, 21089, 21085, 21084, 21063, 21062, 21060, 21053, 21050, 21036, 21037 and 21048, respectively), showed some homology to gene sequences previously identified in humans.

Example 2

ISOLATION AND CHARACTERIZATION OF BREAST TUMOR POLYPEPTIDES OBTAINED BY PCR-BASED SUBTRACTION USING SCID-PASSAGED TUMOR RNA

Human breast tumor antigens were obtained by PCR-based subtraction using SCID mouse passaged breast tumor RNA as follows. Human breast tumor was implanted in SCID mice and harvested on the first or sixth serial passage, as described in Patent Application Serial No. 08/556,659 filed 11/13/95, U.S. Patent No.______. Genes found to be differentially expressed between early and late passage SCID tumor may be stage specific and therefore useful in therapeutic and diagnostic applications. Total RNA was prepared from snap frozen SCID passaged human breast tumor from both the first and sixth passage.

PCR-based subtraction was performed essentially as described above. In the first subtraction (referred to as T9), RNA from first passage tumor was subtracted from sixth passage tumor RNA to identify more aggressive, later passage-specific antigens. Of the 64 clones isolated and sequenced from this subtraction, no significant homologies were found to 30 of these clones, hereinafter referred to as: 13053, 13057, 13059, 13065, 13067, 13068, 13071-13073, 13075, 13078, 13079, 13081, 13082, 13092, 13097, 13101, 13102, 13131, 13133, 13119, 13135, 13139, 13140, 13146-13149, and 13151, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 88-116,

respectively. The isolated cDNA sequences of SEQ ID NO: 117-140 showed homology to known genes.

In a second PCR-based subtraction, RNA from sixth passage tumor was subtracted from first passage tumor RNA to identify antigens down-regulated over multiple passages. Of the 36 clones isolated and sequenced, no significant homologies were found to nineteen of these clones, hereinafter referred to as: 14376, 14377, 14383, 14384, 14387, 14392, 14394, 14398, 14401, 14402, 14405, 14409, 14412, 14414-14416, 14419, 14426, and 14427, with the exception of some previously identified expressed sequence tags (ESTs). The determined cDNA sequences for these clones are provided in SEQ ID NO: 141-159, respectively. The isolated cDNA sequences of SEQ ID NO: 160-174 were found to show homology to previously known genes.

Further analysis of human breast tumor antigens through PCR-based subtraction using first and sixth passage SCID tumor RNA was performed. Sixty three clones were found to be differentially expressed by a two or more fold margin, as determined by microarray analysis, i.e., higher expression in early passage tumor over late passage tumor, or vice versa.. Seventeen of these clones showed no significant homology to any known genes, although some degree of homology with previously identified expressed sequence tags (ESTs) was found, hereinafter referred to as 20266. 20270, 20274, 20276, 20277, 20280, 20281, 20294, 20303, 20310, 20336, 20341, 20941, 20954, 20961, 20965 and 20975 (SEQ ID NO: 252-268, respectively). The remaining clones were found to share some degree of homology to known genes, which are identified in the Brief Description of the Drawings and Sequence Identifiers section above, hereinafter referred to as 20261, 20262, 20265, 20267, 20268, 20271, 20272, 20273, 20278, 20279, 20293, 20300, 20305, 20306, 20307, 20313, 20317, 20318, 20320, 20321, 20322, 20326, 20333, 20335, 20337, 20338, 20340, 20938, 20939, 20940, 20942, 20943, 20944, 20946, 20947, 20948, 20949, 20950, 20951, 20952, 20957, 20959, 20966. 20976, 20977 and 20978. The determined cDNA sequences for these clones are provided in SEQ ID NO: 269-313, respectively.

The clones 20310, 20281, 20262, 20280, 20303, 20336, 20270, 20341, 20326 and 20977 (also referred to as B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P, respectively) were selected for further analysis based

on the results obtained with microarray analysis. Specifically, microarray data analysis indicated at least two- to three-fold overexpression of these clones in breast tumor RNA compared to normal tissues tested. Subsequent studies led to the determination of the complete insert sequence for the clones B820P, B821P, B822P, B823P, B824P, B825P, B826P, B827P, B828P and B829P. These extended cDNA sequences are provided in SEQ ID NO: 416-426, respectively.

Example 3 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on an Perkin Elmer/Applied Biosystems Division 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methylt-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention.

Claims

- 1. An isolated polypeptide comprising at least an immunogenic portion of a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468;
- (b) sequences that hybridize to a sequence of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 under moderately stringent conditions; and
 - (c) a complement of a sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 176, 179, 181 and 469-473.

- 4. An isolated polynucleotide encoding at least 15 contiguous amino acid residues of a breast tumor protein, or a variant thereof that differs in one or more substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 or a complement of any of the foregoing sequences.
- 5. An isolated polynucleotide encoding a breast tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468.
- 7. An isolated polynucleotide comprising a sequence that hybridizes to a sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219,

- 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 under moderately stringent conditions.
- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims claim 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An expression vector comprising a polynucleotide according claim 8.
- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with an immunostimulant.
- 15. A vaccine according to claim 14, wherein the immunostimulant is an adjuvant.
- 16. A vaccine according to claim 14, wherein the immunostimulant induces a predominantly Type I response.

17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.

- 18. A vaccine comprising a polynucleotide according to claim 4. in combination with an immunostimulant.
- 19. A vaccine according to claim 18, wherein the immunostimulant is an adjuvant.
- 20. A vaccine according to claim 18, wherein the immunostimulant induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a breast tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 or a complement of any of the foregoing polynucleotide sequences.
- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

- 23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.
- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with an immunostimulant.
- 26. A vaccine according to claim 25, wherein the immunostimulant is an adjuvant.
- 27. A vaccine according to claim 25, wherein the immunostimulant induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-binding fragment thereof according to claim 21, and thereby inhibiting the development

of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is breast cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.

- 40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.
- 41. A vaccine comprising a fusion protein according to claim 35, in combination with an immunostimulant.
- 42. A vaccine according to claim 41, wherein the immunostimulant is an adjuvant.
- 43. A vaccine according to claim 41, wherein the immunostimulant induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with an immunostimulant.
- 46. A vaccine according to claim 45, wherein the immunostimulant is an adjuvant.
- 47. A vaccine according to claim 45, wherein the immunostimulant induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.
- 49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.

- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOS: 1-175, 178, 180 and 182-468; and
- (ii) complements of the foregoing polynucleotides; wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the antigen from the sample.
- 51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.
- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a breast tumor protein, comprising contacting T cells with one or more of:
 - (i) a polypeptide according to claim 1;
 - (ii) a polynucleotide encoding such a polypeptide; and/or
- (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.
- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.

- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
 - (i) a polypeptide according to claim 1:
 - (ii) a polynucleotide encoding such a polypeptide; or
 - (iii) an antigen-presenting cell that expresses such a

such that T cells proliferate; and

polypeptide;

polypeptide;

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4⁺ and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
 - (i) a polypeptide according to claim 1;
 - (ii) a polynucleotide encoding such a polypeptide; or
 - (iii) an antigen-presenting cell that expresses such a

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:

- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOS: 1-175, 178, 180 and 182-468; and
 - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 59. A method according to claim 58, wherein the binding agent is an antibody.
- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.
- 61. A method according to claim 58, wherein the cancer is breast cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 1-175, 178, 180 and 182-468 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
 - (c) repeating steps (a) and (b) using a biological sample obtained from

the patient at a subsequent point in time; and

- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.
- 65. A method according to claim 62, wherein the cancer is a breast cancer.
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 1-175, 178, 180 and 182-468 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 1-175, 178, 180 and 182-468 or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.

- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
 - 72. A diagnostic kit, comprising:
 - (a) one or more antibodies according to claim 21; and
 - (b) a detection reagent comprising a reporter group.
- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.
- 75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.
- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 contiguous nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a breast tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468 or a complement of any of the foregoing polynucleotides.

78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 contiguous nucleotides recited in any one of SEQ ID NOS: 2, 4-15, 18-33, 35-47, 49-56, 58, 59, 63-73, 88-116, 141-159, 175, 178, 180, 185, 186, 194, 199, 205, 208, 211, 214-216, 219, 222, 226, 232, 236, 240, 241, 245, 246, 252-268, 320-324, 342, 353, 366-368, 377, 382, 385, 389, 395, 397, 400, 408, 411, 413, 414, 416, 417, 419-423, 426, 427, 429, 431, 435-438, 441, 443-446, 450, 453, 454 and 463-468.

- 79. A diagnostic kit, comprising:
- (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.

SEQUENCE LISTING

<110> Corixa Corporation Yuqui, Jiang Dillon, Davin C. Mitcham, Jennifer L. Xu, Jiangchun Harlocker, Susan L. <120> COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE <130> 210121.47001PC <140> PCT <141> 2000-02-15 <160> 474 <170> FastSEQ for Windows Version 3.0 <210> 1 <211> 281 <212> DNA <213> Homo sapien <400> 1 caatgacagt caatctctat cgacagcctg cttcatattt agctattgtt cgtattgcct 60 totgtoctag gaacagtoat atotcaagtt caaatgccac aacctgagaa goggtgggot 120 aagataggtc ctactgcaaa ccacccctcc atatttccgt acgcaattac aattcagttt 180 ctgtgacatc tctttacacc actggaggaa aaatgagata ttctctgatt tattctacta 240 taacactcta catagagcta tggtgagtgc taaccacatc g <210> 2 <211> 300 <212> DNA <213> Homo sapien <400> 2 gaggtcctgg gctaacctaa tggtttatta ttggtggaga gaaagatctg gaaatacttg 60 aggttattac atactagatt agcttctaat gtgaaccatt tttcttttaa cagtgataaa 120 ttattatttc cgaagttaac tgttcccttg gtcgtgatac acactcgatt aacaaacata 180 ctgttgtatt ttttccagtt ttgtttggct atgccaccac agtcatcccc agggtctata catactatgt ctcaactgta ttatttgcca tttttggcat tagaatgctt cgggaaggct <210> 3 <211> 302 <212> DNA <213> Homo sapien <400> 3 ggccgaggta attggttaag tctaaagaga ttattattcc ttgatgtttg ctttgtattg 60 gctacaaatg tgcagaggta atacatatgt gatgtcgatg tctctgtctt tttttttgtc .

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tttgaatttt caatgatagg acttattgga aattggggat aattctgttg tggtattaaa
                                                                       360
taatattcat tttttaaaaa ctcatcttgg tattgagtta gtgcattgac ttccaatgaa
                                                                       420
ttgacataag cccatatttc attttaacca gaaacaaaaa ctagaaaatg ttactcccta
                                                                       480
aataggcaac aatgtatttt ataagcactg cagagattta gtaaaaaaaca tgtatagtta
                                                                       540
ctttagaaac aacttctgac acttgagggt tacccaatgg tctccttccc attctttata
                                                                       600
tgaggtaaat gcaaaccagg gagccaccga ataaacagcc ctgagt
                                                                       646
      <210> 80
      <211> 276
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(276)
      <223> n = A,T,C or G
      <400> 80
gtctgaatga gcttcnctgc gagatgganc ancataaccc agaantccaa aancntanng
                                                                        60
aacgnnaaaa cccgntngaa caagnaaacn gcaactnacg gccgcctgnt gnagggcgag
                                                                       120
gacgcccacc tetecteete ecagttetee tetggatege agneateean agatgtgace
                                                                       180
tcttccagcc gccaaatccg caccaaggtc atggatgtgc acgatggcaa ggtgggtgtc
                                                                       240
cacccacgaa caggtccttc gcaccaagaa ctgagg
                                                                       276
      <210> 81
      <211> 647
      <212> DNA
      <213> Homo sapien
      <400> 81
gtcctgcctt tcatcttttc tttaaaaaaa ataaatgttt acaaaacatt tccctcagat
                                                                        60
tttaaaattc atggaagtaa taaacagtaa taaaatatgg atactatgaa aactgacaca
                                                                       120
cagaaaaaca taaccataaa atattgttcc aggatacaga tattaattaa gagtgacttc
                                                                       180
gttagcaaca cgtagacatt catacatatc cggtggaaga ctggtttctg agatgcgatt
                                                                       240
gccatccaaa cgcaaatgct tgatcttgga gtaggrtaat ggccccagga tcttgcagaa
                                                                       300
gctctttatg tcaaacttct caagttgatt gacctccagg taatagtttt caaggttttc
                                                                       360
attgacagtt ggtatgtttt taagcttgtt ataggacaga tccagctcaa ccagggatga
                                                                       420
cacattgaaa gaatttccag gtattccact atcagccagt tcgttgtgag ataaacgcag
                                                                       480
atactgcaat gcattaaaac gcttgaaata ctcatcaggg atgttgctga tcttattgtt
                                                                       540
gtctaagtag agagttagaa gagagacagg gagaccagaa ggcagtctgg ctatctgatt
                                                                       600
gaagctcaag tcaaggtatt cgagtgattt aagaccttta aaagcag
                                                                       647
      <210> 82
      <211> 878
      <212> DNA
      <213> Homo sapien
      <400> 82
ccttctttcc ccactcaatt cttcctgccc tgttattaat taagatatct tcagcttgta
                                                                       60
gtcagacaca atcagaatya cagaaaaatc ctgcctaagg caaagaaata taagacaaga
                                                                       120
ctatgatatc aatgaatgtg ggttaagtaa tagatttcca gctaaattgg tctaaaaaaag
```

```
aatattaagt gtggacagac ctatttcaaa ggagcttaat tgatctcact tgttttaqtt
                                                                       240
ctgatccagg gagatcaccc ctctaattat ttctgaactt ggttaataaa agtttataag
                                                                       300
atttttatga agcagccact gtatgatatt ttaagcaaat atgttattta aaatattgat
                                                                       360
cettecettg gaccacette atgttagttg ggtattataa ataagagata caaccatqaa
                                                                       420
tatattatgt ttatacaaaa tcaatctgaa cacaattcat aaagatttct cttttatacc
                                                                       480
ttcctcactg gcccctcca cctgcccata gtcaccaaat tctgttttaa atcaatgacc
                                                                       540
taagatcaac aatgaagtat tttataaatg tatttatgct gctagactgt gggtcaaatg
                                                                       600
tttccatttt caaattattt agaattctta tgagtttaaa atttgtaaat ttctaaatcc
                                                                       660
aatcatgtaa aatgaaactg ttgctccatt ggagtagtct cccacctaaa tatcaaqatq
                                                                       720
gctatatgct aaaaagagaa aatatggtca agtctaaaat ggctaattgt cctatgatgc
                                                                       780
tattatcata gactaatgac atttatcttc aaaacaccaa attgtcttta gaaaaattaa
                                                                       840
tgtgattaca ggtagagaac ctcggccgcg accacgct
                                                                       878
      <210> 83
      <211> 645
      <212> DNA
      <213> Homo sapien
      <400> 83
acaaacattt tacaaaaaag aacattacca atatcagtgg cagtaagggc aagctgaaga
                                                                        60
ataaatagac tgagtttccg ggcaatgtct gtcctcaaag acatccaaac tgcgttcaqq
                                                                       120
cagctgaaac aggcttcttt cccagtgaca agcatatgtg gtcagtaata caaacgatgg
                                                                       180
taaatgaggc tactacatag gcccagttaa caaactcctc ttctcctcgg gtaggccatg
                                                                       240
atacaagtgg aactcatcaa ataatttaaa cccaaggcga taacaacgct atttcccatc
                                                                       300
taaactcatt taagccttca caatgtcgca atggattcag ttacttgcaa acgatcccgg
                                                                       360
gttgtcatac agatacttgt ttttacacat aacgctgtgc catcccttcc ttcactgccc
                                                                       420
cagtcaggtt tcctgttgtt ggaccgaaag gggatacatt ttagaaatgc ttccctcaaq
                                                                       480
acagaagtga gaaagaaagg agaccctgag gccaggatct attaaacctg gtgtgtgcgc
                                                                       540
aaaagggagg gggaaggcag gaatttgaaa ggataaacgt ctcctttgcg ccgaggaatc
                                                                       600
aggaagcgtg actcacttgg gtctgggacg ataccgaaat ccggt
                                                                       645
      <210> 84
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(301)
      <223> n = A, T, C or G
      <400> 84
tctgatgtca atcacaactt gaaggatgcc aatgatgtac caatccaatg tgaaatctct
                                                                        60
cctcttatct cctatgctgg agaaggatta gaaggttatg tggcagataa agaattccat
                                                                       120
gcacctctaa tcatcgatga gaatggagtt catgggctgg tgaaaaatgg tatttgaacc
                                                                       180
agataccaag ttttgtttgc cacgatagga atagctttta tttttgatag accaactgtg
                                                                       240
aacctacaag acgtcttgga caactgaagn ttaaatatcc acangggttt attttgcttg
                                                                       300
                                                                       301
      <210> 85
      <211> 296
      <212> DNA
     <213> Homo sapien
     <220>
```

```
<221> misc_feature
       <222> (1)...(296)
       <223> n = A,T,C or G
       <400> 85
 agcgtgggtc gcggcncgan gtagagaacc gactgaaacg tttgagatga agaaagttct
                                                                         60
 cctcctgatc acagccatct tggcagtggc tgttggtttc ccagtctctc aagaccagga
                                                                        120
 acgagaaaaa agaagtatca gtgacagcga tgaattagct tcagggtttt ttgtgttccc
                                                                        180
 ttacccatat ccatttcgcc cacttccacc aattccattt ccaagatttc catggtttan
                                                                        240
 acgtaatttt cctattccaa tacctgaatc tgcccctaca actccccttc ctagcg
                                                                        296
       <210> 86
       <211> 806
       <212> DNA
       <213> Homo sapien
      <400> 86
 totacgatgg coattigctc attgtctttc ctctgtgtgt agtgagtgac cctggcagtg
                                                                        60
 tttgcctgct cagagtggcc cctcagaaca acagggctgg ccttggaaaa accccaaaac
                                                                        120
 aggactgtgg tgacaactct ggtcaggtgt gatttgacat gagggccgga ggcggttgct
                                                                        180
 gacggcagga ctggagaggc tgcgtgcccg gcactggcag cgaggctcgt gtgtccccca
                                                                        240
 ggcagatctg ggcactttcc caacccaggt ttatgccqtc tccagggaaq cctcqqtqcc
                                                                        300
 agagtggtgg gcagatctga ccatccccac agaccagaaa caaggaattt ctgggattac
                                                                        360
ccagtccccc ttcaacccag ttgatgtaac cacctcattt tttacaaata cagaatctat
                                                                        420
 totactcagg ctatgggcct cgtcctcact cagttattgc gagtgttgct gtccgcatgc
                                                                        480
 teegggeece acgtggetee tgtgetetag ateatggtga eteecegee etgtggttgg
                                                                        540
 aatcgatgcc acggattgca ggccaaattt cagatcgtgt ttccaaacac ccttgctgtg
                                                                        600
 ccctttaatg ggattgaaag cacttttacc acatggagaa atatattttt aatttgtgat
                                                                        660
gcttttctac aaggtccact atttctgagt ttaatgtgtt tccaacactt aaggagactc
                                                                        720
 taatgaaagc tgatgaattt tcttttctgt ccaaacaagt aaaataaaaa taaaagtcta
                                                                        780
 tttagatgtt gaaaaaaaa aaaaaa
                                                                        806
      <210> 87
      <211> 620
      <212> DNA
      <213> Homo sapien
      <400> 87
tttttgcatc agatctgaaa tgtctgagag taatagtttc tgttgaattt ttttttgttc
                                                                        60
atttttctgc acagtccatt ctgtttttat tactatctag gcttgaaata tatagtttga
                                                                       120
aattatgaca toottootot tigitättit ootoatgatt gottiggota ticaaagtit
                                                                       180
attitagitt catgiaaatt titgaattgi attitccatt attgigaaaa tagtaccact
                                                                       240
gcaattttaa taggaagttt attgaatcta tagattactt tggataatat ggcacttcaa
                                                                       300
taatattcat gttttcaatt catagacaaa atattttaaa atttatttgt atcttttcta
                                                                       360
attititecti tittitatigi aaagattiac eteetiggit aatatitiee teagaaatti
                                                                       420
attatttaag gtatagtcaa taaaattttc ttcctctatt ttgtcagata gtttaagtgt
                                                                       480
atgaaaccat agatatactt gtatgttaat tttatatttt gctaatttac tqagtgtatt
                                                                       540
tattagttta gagaggtttt aatgtactgt ttatggtttt ttaaatataa gattacttat
                                                                       600
tttttaaaaa aaaaaaaaa
                                                                       620
      <210> 88
      <211> 308
      <212> DNA
```

<213> Homo sapien

```
<220>
      <221> misc_feature
      <222> (1)...(308)
      <223> n = A,T,C or G
      <400> 88
tagctgtgnt cagcaggccg aggtttttt tttttttgag atggagtctc gccctgtcac
                                                                      60
ccaggctgga gtgcagtggc ctgatctcag ctcactgcaa gctccacctc ctggattcac
                                                                     120
gctattctcc tgcctcagcc tcccaagtag ctgggactac aggcgcccgc caccacqccc
                                                                     180
agctaattnt ttgnattttt agtacnagat gcggtttcat cgtgttagcc agcatggnct
                                                                     240
cgatetectg acctegtgaa etgecegeet eggeetecea aagacetgee egggenggee
                                                                     300
gctcgaaa
                                                                     308
      <210> 89
      <211> 492
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(492)
      <223> n = A, T, C or G
      <400> 89
agcggccgcc cgggcaggtc tgttaagtaa catacatatc accttaataa aaatcaagat
                                                                      60
gaaatgtttt agaaactatt ttatcaaaag tggctctgat acaaagactt gtacatgatt
                                                                    . 120
gttcacagca gcactattaa tgccaaaaag tagacaaaac ctaaatgtcc attaactgat
                                                                     180
aagcaaaatg tggtatatcc atacaatgga atattatgta gcccacaaca tggcatggag
                                                                     240
tactacaaca tggatgagcc tcaaaaacgt tatgctaaat gaaaaaagtc agatatagga
                                                                     300
aaccacatgt catatgatcc catttatatg aaatagccag aaaaggcaag tcatagaaac
                                                                     360
aagatagatc ggaaaatggg ttggaggact acaaatggca ccagggatct ttgaagttga
                                                                     420
tggaaatggt ctaaaatcag actgtggntg tggttgaaca agtctgtaaa tttaccaaaa
                                                                     480
tgcgttaata ca
                                                                     492
      <210> 90
      <211> 390
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(390)
     \langle 223 \rangle n = A,T,C or G
     <400> 90
60
gttctctgtt ttattgcaat acagcaaagt ctggttaata ttaagngata tcaacataaa
                                                                    120
gtattggtga ggagtetttt gtgacatttt ttaccatece acettaaata tttetgtgca
                                                                    180
aaanaatcca catcattgtt tggtancana ggatctctta aaaagttccc taanacactg
                                                                    240
agggcataaa accaaacaaa ataaaataag gagtgatagg ctaaagcagt atcttcccct
                                                                    300
ccatccacat ttgncaagca ttatattcta accaaaaaat gatcacacca ggccatgcaa
                                                                    360
aactgtccaa tattaccgag aaaaaaccct
                                                                    390
     <210> 91
```

<211> 192

```
<212> DNA
      <213> Homo sapien
      <400> 91
agcgtggtcg cggccgaggt ctgtcaatta atgctagtcc tcaggattta aaaaataatc
                                                                         60
ttaactcaaa gtccaatgca aaaacattaa gttggtaatt actcttgatc ttgaattact
                                                                       120
tccgttacga aagtccttca catttttcaa actaagctac tatatttaag gcctgcccgg
                                                                       180
gcggccgctc ga
                                                                        192
      <210> 92
      <211> 570
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(570)
      \langle 223 \rangle n = A,T,C or G
      <400> 92
agcgtggtcg cggccgaggt ctgacaacta acaaagaagc aaaaactggc atcttggaca
                                                                        60
tcctagtatt acacttgcaa gcaattagaa cacaaggagg gccaaggaaa aagtttagct
                                                                       120
ttgaatcact tccaaatcta ctgattttga ggttccgcag tagttctaac aaaacttttc
                                                                       180
agacaatgtt aactttcgat taagaaagaa aaaaacccca aacatcttca ggaattccat
                                                                       240
gccaggttca gtctcttcca gtgagcccgc ttgctaaaag tccacgtgca ccattaatta
                                                                       300
gctgggctgg cagcaccatg taaaaagaag cctattcacc accaaccaca cagactagac
                                                                       360
atgtaaagta ggatcaagta atggatgaca accatggtcg tggaatatgg tcaatgagag
                                                                       420
tcagaaaagt acaggcacca gtacaagcag cagataacag aattgacggg ccaaaggata
                                                                       480
aaaataggct tatttaaata ggatgctaca gaacacatnc acttctaatt ggaagctgct
                                                                       540
ttacactggg tggcattgna ccatatgcat
                                                                       570
      <210> 93
     <211> 446
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(446)
      <223> n = A,T,C or G
      <400> 93
tcgagcggcc gcccgggcag gtccaggttt ttatttagtt gtgtaatctt ggacaagtta
                                                                        60
cctaactttt ttgagtctga atatatttaa tctgcaaaat gagaatcatg ataatacgtc
                                                                       120
ataggcttaa ttaggaggat taaatgaaat aatttatagg tggtgccatg gttacataca
                                                                       180
agtattagta gttaattott ttootttgtt tacttttata gtataggttg gatgaaggtt
                                                                       240
ccagtatagg caaaaatact acttgggggt aaagtagagt gtgatacttt atttgaaatg
                                                                       300
ttccctgaat ctgatcttta ctttttgnta ctgctgcact acccaaatcc aaattttcat
                                                                       360
cccaacattc ttggatttgt gggacagcng tagcagcttt tccaatataa tctatactac
                                                                       420
atcttttctt actttggtgc tttttg
                                                                       446
     <210> 94
     <211> 409
     <212> DNA
     <213> Homo sapien
```

```
<400> 94
 cgagcggccg cccgggcagg tccatcagct cttctgctta gaatacgagg cagacagtgg
                                                                         60
 agaggtcaca tcagttatcg tctatcaggg tgatgaccca agaaaggtga gtgagaaggt
                                                                        120
gtcggcacac acgcctctgg atccacccat gcgagaagcc ctcaagttgc gtatccagga
                                                                        180
ggagattgca aagcgccaga gccaacactg accatgttga aggcgttctc tccaggctgg
                                                                        240
attcactgca ctcggaagaa ttctgcccag ggaatttagt gtgggggtac caggaccagt
                                                                        300
ttgtcttgat cttgagaccc ccagagctgc tgcatccata gggtgttgca ggactacacc
                                                                        360
tggcctgcct tgcagtcatt ctttcttata tgttgaccca tttgcccaa
                                                                        409
       <210> 95
       <211> 490
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(490)
      <223> n = A,T,C or G
      <400> 95
tegageggee geeegggeag greetacttg trigeagett ceacacactg cacetaceta
                                                                         60
ctacctctct tccatgctta actgggttta gaaaggtgag ctatgcgtag aagaactact
                                                                        120
tgggatattc aagtgctgta tttgaacgat aagcctatag ataacagtct gaagctgcaa
                                                                        180
gggagacttt gttagtacac tactataaac aggtaaacta cctgtttgta cttgatatag
                                                                        240
tgcatatgaa atgactgatt taatacaaaa ctacagaaca tgcaaaattt tttctgagat
                                                                        300
gttaagtatt acttcagtgg agaacaaaac ttacttaacc tttcgctaat gcatgtagta
                                                                        360
ccagaaagca aacatggttt tagcttcctt tactcaaaat atgaacatta agtggttgtg
                                                                        420
aattttgtct gccaagtggt tcagaaaata cattataaat aacctaagtt aaaaaaaaga
                                                                        480
aactgngaac
                                                                        490
      <210> 96
      <211> 223
      <212> DNA
      <213> Homo sapien
      <400> 96
agcgtggtcg cggccgaggt ctggaagccc accctaggac ttgaatggca ccttgtcctt
                                                                        60
tctctgccag taatgcaatc caacacaata tgctacaggg aaaacagaat ttccacggtg
                                                                       120
ccgccctctg gtacaaggga aacagcacgc aaagcaaaag gccacagagg gctccctgag
                                                                       180
aatccagtac aactaagcga ggacctgccc gggcggccgc tcg
                                                                       223
      <210> 97
      <211> 527
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(527)
      <223> n = A, T, C or G
      <400> 97
tcgagcggcc gcccgggcag gtctgtgcag gagacactga agtgggtagt gtccataatc
                                                                        60
tttttagcct gttgctgaaa ttccagttgt actccttcaa accaaaatgc ttacaggatc
                                                                       120
```

```
atgggaaagc ctcggttgca gaaatcaaga caggcaagtg ggaagataac tcggctttga
                                                                         180
  ggttaaacag atctgggttc aaagcatagt ttcactctct gtcttgtgaa gtgtcctqqq
                                                                         240
  tgaagtcatt tcctctttg aatttcagag aggatgaaaa tataaaaagt ataataacta
                                                                         300
  tcttcataat ctttgtgagg attaaagaag acgaagtgtg tgaaaagcta agcacagagc
                                                                         360
  aggcattcta caataagtag ttattatttt tggaaccatc ccgnccctag ccccagccca
                                                                         420
  attaccttct cttagnctct tcatatcgaa ngccgtaatc ttgaccttct cttgcnactg
                                                                         480
  gattggtgct ggttgatgcc caaacttccc gagatgctgt ctgggaa
                                                                         527
        <210> 98
        <211> 514
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1) ... (514)
        <223> n = A,T,C or G
        <400> 98
  tegageggee geeegggeag gtetggetee catggeeett ggggtggeet gaetetgtea
                                                                          60
 ctattcctaa aaccttctag gacatctgct ccaggaagaa ctttcaacac caaaattcat
                                                                         120
 ctcaatttta cagatgggaa aagtgattct gagaccagac cagggtcagg ccaaggtcat
                                                                         180
 ccagcatcag tggctgggct gagactgggc ccagggaadc ctgtctgctc ctcttttcc
                                                                         240
 cagagetgtg agttetetag ceaaggetge actettgagg gagagecagg aageataget
                                                                         300
 gaggccatga caacctcact cttcacctga aaatttaacc cgtggcagag gatccaggca
                                                                         360
 catatagget teggagecaa acaggaecte ggeegegaec aegetaagee gaatteeage
                                                                         420
 acactggcgg ccgttactag tggatcccga gcttnggtac caagcttggc gtaatcatgg
                                                                         480
 gcatagctgg ttcctggggt gaaaatggta tccg
                                                                         514
       <210> 99
       <211> 530
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(530)
       <223> n = A,T,C or G
       <400> 99
 tcgagcggcc gcccgggcag gtctgaagaa acaggtataa atttggcagc cagtaatttt
                                                                         60
 gacagggaag ttacagcttg catgacttta aatatgtaaa tttgaaaata ctgaatttcg
                                                                        120
. agtaatcatt gtgctttgtg ttgatctgaa aaatataaca ctggctgtcg aagaagcatg
                                                                        180
 ttcaaaaata tttaattcac ttcaaaatgt catacaaatt atggtggttt ctatgcaccc
                                                                        240
 ctaaagcttc aagtcattta gctcaggtac atactaaagt aatatattaa ttcttccagt
                                                                        300
 acagtggtgt ttcataccat tgacatttgc ataccctaga ataatttaag aaagacatgt
                                                                        360
 gtaatattca caatgttcag aaaagcaagc aaaaggtcaa ggaacctgct ttggttcttc
                                                                        420
 tggagatggn ctcatatcag cttcataaac attcattcta caaaatagta agctaaccat
                                                                        480
 ttgaacccca atttccagat taagcatatt ttctcataaa tnatgaagcc
                                                                        530
       <210> 100
       <211> 529
       <212> DNA
       <213> Homo sapien
```

```
<400> 100
agcgtggtcg cggccgaggt ccaggcacgg tggcttatgt gtgtaatccc agcacttggg
                                                                        60
gaggctgagg gaggtggatc acttgagtcc aggagtttga gaccagtctg ggcaacatgg
                                                                       120
cgaaacttca tcactaccaa agaagaaaaa aattagccag gtgtggtggt gtatgcctgt
                                                                       180
agtoccagat actotggtgg otgaggtgag aggatagott gagoccagga aattgaggot
                                                                       240
gcagtgaact atgattgcac tactgtgctc cagcttgggc aacagagtga gatcttqtct
                                                                       300
ccaaaagtcc ttgaaggatt ttaggaagtt gttaaaagtc ttgaaacgat gtttggggc
                                                                       360
atgttagggt tcttgaatgt ttaattcctc taataactgc ttattcaaga gaagcatttc
                                                                       420
tgactgggtg cggggcagtg gcttcatgcc ccataatccc agtactttgg gaggctgaag
                                                                       480
caggaacatt gcttgagccc aggacttcaa gaacagcctg ggtaacata
                                                                       529
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      <211> 277
      <212> DNA
      <213> Homo sapien
      <400> 101
tcgagcggcc gcccgggcag gtcgcaggaa gaggatggaa actgaggagt ccaggaagaa
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gagggaacga gatcttgagc tggaaatggg agatgattat attttggatc ttcagaagta
                                                                       120
ctgggattta atgaatttgt ctgaaaaaca tgataagata ccagaaatct gggaaggcca
                                                                       180
taatataget gattatattg atecageeat catgaagaaa ttggaagaat tagaaaaaga
                                                                       240
agaagagctg agaacagacc tcggccgcga ccacgct
                                                                       277
      <210> 102
      <211> 490
      <212> DNA
      <213> Homo sapien
      <400> 102
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agtcgatggg acagttagag gggatgtgct aaagcgtgaa atcagttgtc cttaattttt
                                                                       120
agaaagattt tggtaactag gtgtctcagg gctgggttgg ggtccaaagt gtaaggaccc
                                                                       180
ectgecetta gtggagaget ggagettgga gaeattaece etteateaga aggaatttte
                                                                       240
ggatgttttc ttgggaagct gttttggtcc ttggaagcag tgagagctgg gaagcttctt
                                                                       300
ttggctctag gtgagttgtc atgtgggtaa gttgaggtta tcttgggata aagggtcttc
                                                                       360
tagggcacaa aactcactct aggtttatat tgtatgtagc ttatattttt tactaaggtg
                                                                       420
teacettata ageatetata aattgaette tttttettag ttgtatgace tgeeceggge
                                                                       480
ggccgctcga
                                                                       490
      <210> 103
      <211> 490
      <212> DNA
     <213> Homo sapien
     <400> 103
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taggtaattt gttcagttca atgtttacaa ttcttatgga aaaaattagc aacacacac
                                                                      120
tttaaaacgt gtgcatttac ctttgcgtga gtgcttaaaa tacatatttc tatttcaaga
                                                                      180
tgacatttaa aaattattet aatatateag eageaaaaat ataatttgea attacaaaaa
                                                                      240
actaaactag aatccttaag ttattctcat gtttacagtt gtgattcttt aataaatact
                                                                      300
attatgcage tetattgttt aagetttetg gatttggttt aaacacatge atatattg
                                                                      360
tcaattgtgg gaagctttac aagttatatt ccatgcactt tttggacaga gttctaacag
                                                                      420
agccagccag tccacaaaac aggcaagaca aaagttgaat taactggggc aaaataggac
                                                                      480
tcttatgcaa
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<212> DNA

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<210> 104
      <211> 489
      <212> DNA
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      <400> 104
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                                                                        120
ttaatgtcag actaggccag agtttctcaa tctttttatt ctcacttccc aaaggagccq
                                                                        180
ttggagattt tcccctcaat ctctctctt catgaaattt cataccacaa atatagtatg
                                                                        240
ttttatttat gtactgtgac cctttgaagg atcacaaacc aatataatag tttttcttt
                                                                       300
taacccgtca aggaccaagt ttttgcccct gttggaaatg cataaactgg actgatgaat
                                                                       360
tggtatagat ggcttttatc atgaggatca gaaaaacttg aaattccttg gctacgacac
                                                                       420
tccatattta tcaccgtata gggaggacct tggtatgggg aagtagaaac acttctacac
                                                                       480
tttacagca
                                                                       489
      <210> 105
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A,T,C or G
      <400> 105
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aaaataattg cacctccctc tgctgcttat tcccttccgt ttttcatttg agtgtgaaca
                                                                       120
gttagataaa atctgtggct gnctcttcca ccttgctcta gtttccattg ctgtgagcaq
                                                                       180
gccctcctat gccccgcatt tagctacaat gctgtggact cacttgattc tttttctccg
                                                                       240
agetttgtet agaaatatgt gaaggtgagg ttaagtgett etetgtgtag atecaettag
                                                                       300
ccctgtctgc tgtctcgatg ggcgttgctt cgtctctcct ctcttccatc ctttccattt
                                                                       360
gcttctcacc accttctggc ttcttttctt aatgcaataa aggcagtttc taacaaagaa
                                                                       420
agaatgtggg ctttggagtt agacagacct ggntttaaat tctgcttctg gctctccaa
      <210> 106
      <211> 511
      <212> DNA
      <213> Homo sapien
      <400> 106
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agttggacct gcagtagtat gggaagctca cggcctaaat accgactgcc ctctgacccc
                                                                       120
accgtccagc gattctagaa catttctagt aggaaagaca tagcaaggga ttttcatgat
                                                                       180
tgggaaatac tgggagacaa gctgaagatt tgttaagggc tatgcttctg tcatctttta
                                                                       240
ggtatttaag gctactcctt tagctagcta ctttgagctg tttaaagtga ctatctccct
                                                                       300
acacagagtt acacaatgag catctctgaa agagaatatt accctggatt tccaaagatg
                                                                       360
tactctaaca ggatgaccag gcaaaaggtg acccggggga ggagtctgtt ataacactcg
                                                                       420
gacccacatg ttctcaaggc acttcagaac tttgggaaat cattttgtac cggatcctca
                                                                       480
gaaagcattt atggaaatac acatccttta g
                                                                       511
      <210> 107
      <211> 451
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<213> Homo sapien <400> 107 ggccgcccgg gcaggtccag aatatcaaat caaaaggtca caaatgttca Cttcctcctc 60 caccccctta catattggat cttcaattgc aatagggagt gtaagatggg cattttagag 120 acgtagttgc atcagcagaa gcaaacccat cttatacaaa tgggttttgg ggataggaaa 180 aggctgctaa aaattcacaa gtcaccattc cccagaagca atgaatagcc gtagaagacc 240 aaggaagatc aacaagtttc caaagtgcta aagccagaga tttggccctt ccaaaatacc 300 accaggacge etggaceegt gggeteteeg catgteacea etgactgeea ggatgetget 360 gcacctccct tccttgagac acaacagaga gacagtgaag tcacccaaga ctgggatcat 420 cagaggetee teatgettge tacagagaag e 451 <210> 108 <211> 461 <212> DNA <213> Homo sapien <400> 108 ccgcccgggc aggtcctgaa aacattcaga ctaatcaaaa tggtactact gtaacttctt 60 ataatacata atataaaagt ttttgaaaga tatagacaca attaacccct aaacaacaca 120 ctatctgatt ctcaaaagca atggctattt aacaagatgt aaaaggacaa taacatatca .. 180 aagaactttc acacacctaa agatagcatt tagcagcaag ttagtcagac aaaacaaaca 240 caaatatttt cacatttcct atgtttgttt ttaactttac ttcataaagc cactgataat 300 tgaggtttct ttcaagtata agatttctaa aattaaaaac tgtttttgac atatttttat . 360 aaagaaataa aaagcaaaac gcaatccaac tatttatatg agtccctctt ctccaacagc 420 tttagatggt tttctgagta cttttttaca cagaatattt t 461 <210> 109 <211> 441 <212> DNA <213> Homo sapien <400> 109 ggccgcccgg gcaggtctga ttataagaga aagaaatcca gtgacacgag ggcaggcagg 60 eccegetetg etetgatega gaaaagette etgatgteag ggagatggaa etgecaceat 120 cagaaccatg gcactttggg tgaaggtgtg tcagcgacca agggggcagg aaatgggcag 180 tgactaaggg ggcaggaaac aggcaggcac atggcaaggt tctcccagcc catcagccca 240 gtgatggcct cgattttgaa gctgcactac tgtctgaaaa gcacaattac tggtgactct 300 taacaaactt cagcatactg gggaaggaga ctgtcaagta actgaattgg aaagatgaaa 360 aagaaccatc totaaaagtt gatgottgto agaagaataa cotcotttgt goaagtottg 420 caacatcttc attcaaccac a 441 <210> 110 <211> 451 <212> DNA <213> Homo sapien <220> <221> misc_feature <222> (1) ... (451) <223> n = A,T,C or G<400> 110 ggtcgcggcc gaggtctggg gaaggggtga gaatccctgg gccttgccca gtcctgagct 60 ctgggtgtct gcagggaagc acagtggtga gttagtgtta aagaaagcat ccagagaggt 120

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aagaggggct tgggtagcac cctttgcctc tgtcacttcc gcaaaaactt cttgttgagg
                                                                        180
 aggaagatga gaaggttgac attgactttg gccttgttga agagtttcat gacagccaca
                                                                        240
 ccctcatact ggagctgcan gagatcctga tagtgaagct tgaaatcgct ccatgtccac
                                                                        300
 acccaggaac tiggcattia citcaaacti tccigccica tcicccggcg tgatgicaaa
                                                                        360
 natgacgttt cttgaagtga gaggcgggaa agatcttcaa tttccaccaa agacaccctt
                                                                        420
 tttccaggaa gcttgagcaa caagtgtaat g
                                                                        451
       <210> 111
       <211> 407
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(407)
      <223> n = A,T,C or G
      <400> 111
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actgcagaca gtggcccang gcaaagagtg tgcgtcatcg atganattgg naagatggag
                                                                        120
ctcttcagtc agnttttcat tcaagctgnt cgtcagacgc tgtctacccc agggactata
                                                                        180
atcctnggca caatcccagt tcctanagga aagccactgn ctcttgtaga agaaatcana
                                                                        240
cacanaaagg atgtgaacng tgtttaatgt caccaaggga aaacatgaaa ccaccttctg
                                                                        300
ccagatatcg ggacgttgcg tgcagatcaa gcacgnaagt gaagacgcgt gcattccttg
                                                                        360
ccttccgtga acgantgccc agntcaagaa gancctgatg gaaccct
                                                                        407
      <210> 112
      <211> 401
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (401)
      <223> n = A,T,C or G
      <400> 112
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cgtcttaacc acttctgtat tgtgtggttt taactgccta aggcggcaat gggcagtggg
                                                                       120
cccctttccc ttaggatggg tatcaattca acaatattta taaggcattt actgtgtgct
                                                                       180
aagcatttgg aagacccagg ctacaaaata agacatagtt cctgccctcc aggccagcag
                                                                       240
agggaggcac aaatacccag gaatctctga tgggtgtgaa gtgcggtcgt gggccacaga
                                                                       300
aaatgaccgt catggagacc ctgctaaagg tcggaccctg agcccaaagg ggtattcaga
                                                                       360
agnggagatg attttggccc cactcataga tgggtggcaa a
                                                                       401
      <210> 113
      <211> 451
      <212> DNA
      <213> Homo sapien
      <400> 113
gtcgcggccg aggtccatat taaaaagtcc atcataaaca aagactcctc ctcatggtat
                                                                        60
gaatatgctc catatgccca taatggtgca taacggactt agaaattcca atgagtctta
                                                                       120
gggttgaaat ttccaatgac ctgagcaagg cagctcccta tagcttctgg ataacatttt
                                                                       180
acacccagag ttcaggctta aacagaccta tcaacacaat tattttcgga ttgtctqtct
                                                                       240
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agaaaacggc aatgctcaaa ggaatataaa taagggtggg gggacatatg cttccagcct
                                                                        300
 ggcctttctc catgtggtaa aaaacaatgg aatggctgtg ttaattttt tttaatcttt
                                                                        360
 tctgaccttt actatgtttg gtaatggaaa taagtcaggg aaaacaaaat gaacaggtct
                                                                        420
 catcacttaa ttaatactgg gttttcttct t
                                                                        451
       <210> 114
       <211> 441
       <212> DNA
       <213> Homo sapien
       <400> 114
ggccgcccgg gcaggtccat cctgtcagag atgggagaag tcacagacgg aatgatggat
                                                                         60
acaaagatgg ttcactttct tacacactat gctgacaaga ttgaatctgt tcattttca
                                                                        120
gaccagttct ctggtccaaa aattatgcaa gaggaaggtc agcctttaaa gctacctgac
                                                                        180
actaagagga cactgttgtt tacatttaat gtgcctggct caggtaacac ttacccaaag
                                                                        240
gatatggagg cactgctacc cctgatgaac atggtgattt attctattga taaaqccaaa
                                                                       300
aagttccgac tcaacagaga aggcaaacaa aaagcagata agaaccgtgc ccgagtagaa
                                                                        360
gagaacttct tgaaacttga cacatgtgca aagacaggaa gcagcacagt ctcggcggga
                                                                        420
ggaagaaaaa aagaacagag a
                                                                        441
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      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(431)
      <223> n = A,T,C or G
      <400> 115
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taatgctgat tagttagaag aaagggctag gattgagaaa gtaccaggaa cttttaatta
                                                                       120
tttaaaagag aatgctgact gttaatgttt taaatcttac tgttcaaatg tactaatatg
                                                                       180
aatttttacc ctttgtgcat gaatattcta aacaactaga agacctccac aatttagcag
                                                                       240
tratgaaagt taaacttttt attataaaaa ttctaaacct tactgctcct ttaccaggaa
                                                                       300
catgacacac tatttancat cagttgcata cctcgccaat agtataattc aactgtcttg
                                                                       360
eccgaacaat catetecate tggaagacgt aageetttag aaacacattt ttetattaat
                                                                       420
ttctctagaa c
                                                                       431
      <210> 116
      <211> 421
      <212> DNA
      <213> Homo sapien
      <400> 116
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aggcagagtg gtgtcaaatc tttgacggca cagatgcctg tgtgactccg gttctgactt
                                                                       120
ttgaggaggt tgttcatcat gatcacaaca aggaaccggg gctcgtttat caccagtgag
                                                                       180
gagcaggacg tgagcccccg ccctgcacct ctgctgttaa acaccccagc catcccttct
                                                                       240
ttcaaaaggg atcctttcat aggagaacac actgaggaga tacttgaaga atttggattc
                                                                       300
agcccgcgaa gagatttatc aagcttaact cagataaaat cattgaaagt aataaggtaa
                                                                       360
aagctaagtc tctaacttcc aggcccacgg ctcaagtgaa tttcgaatac tgcatttaca
                                                                       420
                                                                       421
```

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<210> 117
      <211> 489
      <212> DNA
      <213> Homo sapien
      <400> 117
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                                                                     60
gagggctaaa tccatgaagt ttgtggatgg cctgatgatc cacagcggag accctgttaa
                                                                    120
ctactacgtt gacactgctg tgcgccacgt gttgctcaga cagggtgtgc tgggcatcaa
                                                                    180
ggtgaagatc atgctgccct gggacccaac tggtaagatt ggccctaaga agcccctgcc
                                                                    240
tgaccacgtg agcattgtgg aacccaaaga tgagatactg cccaccaccc ccatctcaga
                                                                    300
acagaagggt gggaagccag agccgcctgc catgccccag ccagtcccca cagcataaca
                                                                    360
gggtctcctt ggcagacctg cccgggcgc cgctcgaaag cccgaattcc agcacactgg
                                                                    420
cggccgttac tagtggatcc cagctcggta ccaagcttgg cgtaatcatg gtcatagctg
                                                                    480
gtttcctgt
                                                                    489
      <210> 118
      <211> 489
      <212> DNA
      <213> Homo sapien
      <400> 118
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                                                                     60
acctgctgct tcaaaacatg atcctttctt actaatatct tgatagtcgg tccatagagc
                                                                    120
attagaaagc aattgactct taaataaaca gaaaagtgcc taatgcacat taaatgaatg
                                                                    180
gcctaactac tggaacttta gtagttctat aaggtgatta acataggtag gatccagttc
                                                                    240
ctatgacagg ctgctgaaga acagatatga gcatcaagag gccattttgt gcactgccac
                                                                    300
cgtgatgcca tcgtgtttct ggatcataat gttcccatta tctgattcta gacacaccac
                                                                    360
aggaatatca gtggggtcag aggttagctt agctgcttgc tgggctagaa cagatatcac
                                                                    420
tecageatge teatetgaca gggteeegeg geaacceaga ttaagteett gtgaatetgt
                                                                    480
gcacaggga
                                                                    489
     <210> 119 ·
     <211> 181
     <212> DNA
     <213> Homo sapien
     <400> 119
taggttccag agacttttgg cccaggagga atatttactt ttagctctgg acatcattac
                                                                     60
aaaaaggaat atttcccaaa cctcttcaga ccgagaatac atgggtaaaa ttattaaata
                                                                    120
180
t
                                                                    181
     <210> 120
     <211> 489
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(489)
     <223> n = A,T,C or G
     <400> 120
gcgtggtcgc ggccgaggtc catttaaaac aaagaaaaat actaaagcca ctagtaaaca
                                                                     60
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tctgatgtgc aaaatacaac atcctctagt tggctttatg ccattattac ataagctcca
                                                                      120
 aatagctcat cttaaattaa aaagaaaaag tggctgtccc atctctgctg cataaatcag
                                                                      180
 240
 tcacagagaa tacaaattta gcaatttaat ttcccaaagc tctttgaaga agcaagagag
                                                                      300
 tctctcttct taatgcagtg ttctcccaag aggaactgta attttgcttg gtacttatgc
                                                                      360
 tgggagatat gcaaaatgtg tttttcaatg tttgctagaa tataatggtt cctcttcagt
                                                                      420
 gnctggttca tcctggaact catgggttaa gaaggacttc ttggagccga actgcccggg
                                                                      480
 cgggccntt
                                                                      489
      <210> 121
      <211> 531
      <212> DNA
      <213> Homo sapien
      <400> 121
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                                                                      -60
atttgatgat gcgtcacctg gaaagcaaaa ggaaatccaa gaaccagatc ctacctatga
                                                                      120
agaaaaaatg caaactgacc gggcaaatag attcgagtat ttattaaagc agacagaact
                                                                      180
ttttgcacat ttcattcaac ctgctgctca gaagactcca acttcacctt tgaagatgaa
                                                                      240
accagggcgc ccacgaataa aaaaagatga gaagcagaac ttactatccg ttggcgatta
                                                                     300
ccgacaccgt agaacagagc aagaggagga tgaagagcta ttaacagaaa gctccaaagc
                                                                     360
aaccaatgtt tgcactcgat ttgaagactc tccatcgtat gtaaaatggg gtaaactgag
                                                                     420
agattatcag gtcccgagga ttaaactggc tcatttcttt gtatgagaat ggcatcaatg
                                                                     480
gtatccttgc agatgaaatg ggcctaggaa agactcttca acaatttctc t
                                                                     531
      <210> 122
      <211> 174
      <212> DNA
      <213> Homo sapien
      <400> 122
tegageggee geeegggeag gtetgeeaac ageagaggeg gggeeteegg catetteaaa
                                                                      60
gcacctctga gcaggeteca gecetetgge tgegggaggg gtetggggte teetetgage
                                                                     120
teggeageaa ageagatgtt atttetetee egegaeeteg geegegaeea eget
                                                                     174
      <210> 123
      <211> 531
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(531)
      <223> n = A,T,C or G
      <400> 123
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tggctcatgc cagcagagct ctctcctcgt ccagcaggcg ccatgcaagg gcaggctaaa
                                                                     120
agacctccag tgcatcaaca tccatctagc anagagaaaa ggggcactga agcagctatg
                                                                     180
tctgccaggg gctaggggct cccttgcaga cagcaatgct acaataaagg acacagaaat
                                                                     240
gggggaggtg ggggaagccc tatttttata acaaagtcaa acagatctgt gccgttcatt
                                                                     300
cccccagaca cacaagtaga aaaaaaccaa tgcttgtggt ttctgccaag atggaatatt
                                                                     360
ceteetteet aanttecaca catggeegtt tgeaatgete gacageattg cactgggetg
                                                                     420
cttgtctctg tggtctgggc accagtagct tgggccccat atacacttct cagttcccac
                                                                     480
anggettatg geenanggge angeteeaat ttteaageae caegaaggaa g
                                                                     531
```

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<210> 124
       <211> 416
       <212> DNA
       <213> Homo sapien
       <400> 124
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                                                                         60
 acttaccaag cccaggaata atgactttta aagccttgaa tatcaactaa gacaaattat
                                                                        120
 gccaattctg atttctcaca tatacttaga ttacacaaag ataaagcttt agatgtgatc
                                                                        180
 attgtttaat gtagacttat ctttaaagtt tttaattaaa aactacagaa gggagtaaac
                                                                        240
 agcaagccaa atgatttaac caaatgattt aagagtaaaa ctcactcaga aagcattata
                                                                        300
 cgtaactaaa tatacatgag catgattata tacatacatg aaactgcaat tttatggcat
                                                                        360
 tctaagtaac tcatttaagt acatttttgg catttaaaca aagatcaaat caagct
                                                                        416
       <210> 125
       <211> 199
      <212> DNA
       <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(199)
      <223> n = A, T, C or G
      <400> 125
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                                                                        60
aggggaaggc coctititat taaactigta cattitacti toottottto anaatgctaa
                                                                       120
taaaaaactt ttgtttatac ttaaaaaaac cataaatcan acaaacaaaa gaaacgattc
                                                                       180
caacatcact tctgngatg
                                                                       199
      <210> 126
      <211> 490
      <212> DNA
      <213> Homo sapien
      <400> 126
cgtggtcgcg gccgaggtcc agttgctcta agtggattgg atatggttgg agtggcacag
                                                                        60
actggatctg ggaaaacatt gtcttatttg cttcctgcca ttgtccacat caatcatcag
                                                                       120
ccattcctag agagaggcga tgggcctatt tgtttggtgc tggcaccaac tcgggaactg
                                                                       180
gcccaacagg tgcagcaagt agctgctgaa tattgtagag catgtcgctt gaagtctact
                                                                       240
tgtatctacg gtggtgctcc taagggacca caaatacgtg atttggagag aggtgtggaa
                                                                       300
atctgtattg caacacctgg aagactgatt gactttttag agtgtggaaa aaccaatctg
                                                                       360
agaagaacaa cctaccttgt ccttgatgaa gcagatagaa tgcttgatat gggctttgaa
                                                                       420
ccccaaataa ggaagattgt ggatcaaata agacctgata ggcaaactct aatgtggagt
                                                                       480
gcgacttggc
                                                                       490
      <210> 127
      <211> 490
      <212> DNA
      <213> Homo sapien
      <400> 127
cgtggtcgcg gccgaggtcg gccgaggtct ggagatctga gaacgggcag actgcctcct
                                                                        60
caagtgggtc cctgacccct gacccccgag cagcctaact gggaggcacc ccccagcagg
                                                                       120
```

```
ggcacactga cacctcacac ggcagggtat tccaacagac ctgaagctga gggtcctgtc
                                                                   180
 tgttagaagg aaaactaaca agcagaaagg acagccacat caaaaaccca tctgtacatc
                                                                   240
 300
 aaactggaaa ctctaaaaag cagagcacct ctcctcttcc aaaggaacgc agttcctcac
                                                                   360
 cagcaatgga acaaagctgg atggagaatg actttgacga gctgagaaaa gaacgcttca
                                                                   420
 gacgatcaaa ttactctgag ctacgggagg acattcaaac caaaggcaaa gaagttgaaa
                                                                   480
 actttgaaaa
                                                                   490
      <210> 128
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(469)
      <223> n = A,T,C or G
      <400> 128
60
ttttttctnt ttattgttac atacaatgta taaacacata aaacanaaaa cagtagggat
                                                                   120
cctctaggat ctctagggan acagtaaagt anaaagaggt ctcanaaaca ttttttaaa
                                                                   180
gtacaagaca ttcagngctc ggcccaaagg cgtaaaaggt ttanagccag canatagctg
                                                                   240
nactaeaggc tecgtetnin tececanage caggacaace ccagggaget niceatiage
                                                                   300
agccagtcca cgcaggcagg atgctgcgga aaaagctcta tgctganaac attccccttg
                                                                   360
atggaaagaa gggcaacaca aaaggggtaa ctaanagctc cttcctctcg tgagggcgac
                                                                   420
aactgaggaa cagaaaagga gtgtcccatg tcacttttga cccctccc
                                                                   469
      <210> 129
      <211> 419
      <212> DNA
      <213> Homo sapien
      <400> 129
gcgtggtcgc ggccgaggtc tgattttcat ttaaatattt cagagctata gcatttgcct
                                                                   60
ccatgctcaa atccacacca ttggggctta agccgctcat gccaacatta gcaaatgaca
                                                                   120
tgcagtttaa tccagagatc actgcttctg ggctgatgca tgccaacaca ctggcgtgat
                                                                   180
ccacgttatg tgcatttttc ttcactttag tgggagaatc aatttttact ccaaggcttc
                                                                   240
ttagttgctt aagagttgca ttaaggacac aatctttgtc caccagtctt gaatgatgtg
                                                                  300
tttttttttt tgtatggtaa acgttttggg ttctggtgca ttcatgactg ataattactg
                                                                  360
ctttggtaga cggctgctca agtttccttg gaggaactat ttaataggtg ggttacttg
                                                                  419
     <210> 130
      <211> 354
     <212> DNA
     <213> Homo sapien
     <400> 130
agcgtggtcg cggccgaggt ccatctgagg agataaccac atcactaaca aagtgggagt
                                                                   60
gaccccgcag agcacgctgt ggaattccat agttggtctc atccctggtc agtttccaca
                                                                  120
tgatgatggt cttatctcga gaggcggaga ggatcatgtc cgggaactgc ggggtagtag
                                                                  180
cgatctgggt tacccagccg ttgtggccct tgagggtgcc acgaagggtc atctgctcag
                                                                  240
tcatggcggc ggcgagagcg tgtgtcgctg cagcgacgag gatggcactg gatggcttag
                                                                  300
agaaactagc accacaacct ctcctgccgc acctgcccgg gcggcccgct cgaa
                                                                  354
```

```
<210> 131
       <211> 474
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(474)
       <223> n = A, T, C or G
       <400> 131
 cgagcggccg cccgggcagg tctggcagca gcttcctctg gaataattga cagctttgtg
                                                                       60
 ctgcctgact aaaatttgaa atgacaaccg ctgaatgtaa aatgatgtac ctacaatgag
                                                                      120
 180
 gaaaacaaac ttattttaaa ccaaagaaac aaatgtatcc aaaatatagt ccatgatata
                                                                      240
 tttgattact agtataacca cagttgaaaa cttaaaaaaa aaaattgaca ttttttgtaa
                                                                      300
 tgggtactaa tggatttata aaaggtttct gtttccaaag atgttattgg ggtccacata
                                                                      360
 ttccttgaag acttcagcat cccaaagccc gacatcagag atactttcct ttagccattg
                                                                      420
 nttcccgtaa cttgcccact ccatggtgat gtgacaggct tcccttcatt agca
                                                                      474
       <210> 132
       <211> 474
      <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(474)
       \langle 223 \rangle n = A,T,C or G
       <400> 132
 ggccgaggtg gggaattcat gtggaggtca gagtggaagc aggtgtgaga gggtccagca
                                                                       60
 gaaggaaaca tggctgccaa agtgtttgag tccattggca agtttggcct ggccttagct
                                                                      120
 gttgcaggag gcgtggtgaa ctctgcctta tataatgtgg atgctgggca cagagctgtc
                                                                      180
 atctttgacc gattccgtgg agtgcaggac attgtggtag gggaagggac tcattttctc
                                                                      240
 atcccgtggg tacagaaacc aattatcttt gactgccgtt ctcgaccacg taatgtgcca
                                                                      300
 gtcatcactg gtagcaaaga tttacagaat gtcaacatca cactgcgcat cctcttccgg
                                                                      360
 cctgtcgcca gccagcttcc tcgcatcttc accagcatcg ganaggacta tgatgaaccg
                                                                      420
tgtgctgccg tccatcacaa ctgagatcct caagtcagtg gtggctcgct ttga
                                                                      474
       <210> 133
       <211> 387
       <212> DNA
       <213> Homo sapien
      <400> 133
 tgctcgagcg gccgccagtg tgatggatat ctgcagaatt cggcttagcg tggtcgcggc
                                                                      60
cgaggtctgc gggcccctta gcctgccctg cttccaagcg acggccatcc cagtagggga
                                                                      120
ctttcccaca ctgtgccttt acgatcagcg tgacagagta gaagctggag tgcctcacca
                                                                      180
cacggcccgg aaacagcggg aagtaactgg aaagagcttt aggacagctt agatgccgag
                                                                      240
tgggcgaatg ccagaccaat gatacccaga gctacctgcc gccaacttgt tgagatgtgt
                                                                      300
gtttgactgt gagagagtgt gtgtttgtgt gtgtgttttg ccatgaactg tggccccagt
                                                                      360
gtatagtgtt tcagtggggg agaactg
                                                                     387
```

```
<211> 401
       <212> DNA
       <213> Homo sapien
       <400> 134
 ggccgcccgg gcaggtctga tgaagaacac gggtgtgatc cttgccaatg acgccaatgc
                                                                         60
 tgagcggctc aagagtgttg tgggcaactt gcatcggctg ggagtcacca acaccattat
                                                                        120
 cagccactat gatgggcgcc agttccccaa ggtggtgggg ggctttgacc gagtactgct
                                                                        180
 ggatgctccc tgcagtggca ctggggtcat ctccaaggat ccagccgtga agactaacaa
                                                                        240
 ggatgagaag gacatcctgc gcttgtgctc acctccagaa ggaagttgct cctgagtgct
                                                                        300
 attgactett greaatgega certeaagae aggaggerae erggritaer geacetgire
                                                                        360
tatcacagtg agacctctgc catggcagaa caggggaagc t
                                                                        401
      <210> 135
      <211> 451
      <212> DNA
      <213> Homo sapien
      <400> 135
ggtcgcggcc gaggtctgtt cctgagaaca gcctgcattg gaatctacag agaggacaac
                                                                         60
taatgtgagt gaggaagtga ctgtatgtgg actgtggaga aagtaagtca cgtgggccct
                                                                       120
tgaggacctg gactgggtta ggaacagttg tactttcaga ggtgaggtgt cgagaaggga
                                                                       180
aagtgaatgt ggtctggagt gtgtccttgg ccttggctcc acagggtgtg ctttcctctg
                                                                       240
gggccgtcag ggagctcatc ccttgtgttc tgccagggtg gggtaccggg gtttgacact
                                                                       300
gaggagggta acctgctggc tggagcggca gaacagtggc cttgatttgt cttttggaag
                                                                       360
attttaaaaa ccaaaaagca taaacattct ggtccttcac aatgctttct ctgaagaaat
                                                                       420
acttaacgga aggacttctc cattcaccat t
                                                                       451
      <210> 136
      <211> 411
      <212> DNA
      <213> Homo sapien
      <400> 136
ggccgcccgg gcaggtctga atcacgtaga atttgaagat caagatgatg aagccagagt
                                                                        60
tcagtatgag ggttttcgac ctgggatgta tgtccgcgtt gagattgaaa atgttccctg
                                                                       120
tgaatttgtg cagaactttg acccccttta ccccattatc ctgggtggct tgggcaacag
                                                                       180
tgagggaaat gttggacatg tgcaggtggg tccctttgct gcgtatttgg tgcctgaggc
                                                                       240
totgtggatt toccotocat caatcatott accototoat coccotoaga tgcgtotgaa
                                                                       300
gaaacatctc tggtataaga aaatcctcaa gtcccaagat ccaatcatat tttctgtagg
                                                                       360
gtggaggaag tttcagacca tcctgctcta ttatatccga agaccacaat g
                                                                       411
      <210> 137
      <211> 211
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(211)
      <223> n = A,T,C or G
      <400> 137
cggccgcccg ggcaggtcgg ttggtgcggc ctccattgtt cgtgttttaa ggcgccatga
                                                                        60
ggggtgacag aggccgtggt cgtggtgggc gctttggttc cagaggaggc ccaggaggag
                                                                       120
```

```
ggttcaggcc ctttgcacca catatcccat ttgacttcta tttgtgtgaa atggcctttc
                                                                        180
cccggntcaa gccagcacct cgatgaaact t
                                                                        211
      <210> 138
      <211> 471
      <212> DNA
      <213> Homo sapien
      <400> 138
gccgcccggg caggtctggg ctggcgactg gcatccaggc cgtaactqca aatctatqct
                                                                        60
aggeggggte tecettetgt gtgtteaagt gttetegaet tggattetta actattttaa
                                                                        120
aaaatgcact gagtttgggt taaaaaccaa ccaccaaaat ggatttcaac acagctctaa
                                                                        180
agccaagggc grggccggct ctcccaacac agcgactcct ggaggccagg rgcccatggg
                                                                        240
cctacatccc ctctcagcac tgaacagtga gttgattttt ctttttacaa taaaaaaagc
                                                                        300.
tgagtaatat tgcataggag taccaagaaa ctgcctcatt ggaaacaaaa actatttaca
                                                                        360
ttaaataaaa agcctggccg caggctgcgt ctgccacatt tacagcacgg tgcgatgcac
                                                                        420
acggtgacca aaccacggag gcaagcttct ggcactcaca ccacgacccg c
                                                                        471
      <210> 139
      <211> 481
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(481)
      <223> n = A,T,C or G
      <400> 139
gtcgcggccg aggtctgttc tttagctcag atttaaacct gctgtctctt ctttatttgc
                                                                        60
agaatgaatt cccagttcct gagcagttca agaccctatg gaacgggcag aagttggtca
                                                                       120
ccacagtgac agaaattgct ggataagcga agtgccactg ggttctttgc cctcccttca
                                                                       180
caccatggga taaatctgta tcaagacggt tcttttctag atttcctcta cctttttgct
                                                                       240
cttaaaactg cttctctgct ctgagaagca cagctacctg ccttcactga aatatacctc
                                                                       300
aggotgaaat ttggggtggg atagoaggto agttgatott otgoaggaag gtgcagottt
                                                                       360
tccatatcag ctcaaccacg ccgncagtcc attcttaagg aactgccgac taggactgat
                                                                       420
gatgcatttt agcttttgag cttttggggg gtattctacc aaccaacagt ccatttggaa
                                                                       480
                                                                       481
      <210> 140
      <211> 421
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (421)
      <223> n = A.T.C or G
      <400> 140
gtcgcggccg aggtttccca tttaagaaaa atagatcttg agattctgat tcttttccaa
                                                                        60
acagtcccct gctttcatgt acagcttttt ctttacctta cccaaaattc tggccttgaa
                                                                       120
gcagttttcc tctatggctt tgcctttctg attttctcag aggctcgagt ctttaatata
                                                                       180
accccaaatg aaagaaccaa ggggaggggt gggatggcac ttttttttgt tggtcttgtt
                                                                       240
ttgttttgtt ttttggttgg ttgggttccg ttatttttta agattagcca ttctctgctg
                                                                       300
```

```
statticect acataatgic aatittiaac cataatitig acatgatiga gatgiactig
                                                                       360
aggetttttt gntttaartg agaaaagaer ttgeaatttt ttttttagga tgageetete
                                                                       420
                                                                       421
       <210> 141
      <211> 242
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(242)
      <223> n = A,T,C or G
      <400> 141
cgantngccc gcccgggcan gtctgtctaa ntttntcang gaccacgaac agaaactcgt
                                                                        60
gcttcaccga anaacaatat cttaaacatc gaanaattta aatattatga aaaaaaacat
                                                                       120
tgcaaaatat aaaataaata nnaaaaggaa aggaaacttt gaaccttatg taccgagcaa
                                                                       180
atccaggtct agcaaacagt gctagtccta nattacttga tntacaacaa cacatgaata
                                                                       240
                                                                       242
      <210> 142
      <211> 551
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(551)
      <223> n = A,T,C or G
      <400> 142
agcgtggtcg cggcncgang tccacagggc anatattctt ttagtgtctg gaattaaaat
                                                                        60
gtttgaggtt tangtttgcc attgtctttc caaaaggcca aataattcan atgtaaccac
                                                                       120
accaagtgca aacctgtgct ttctatttca cgtactgttg tccatacagt tctaaataca
                                                                       180
tgtgcagggg attgtagcta atgcattaca cagtcgttca gtcttctctg cagacacact
                                                                       240
aagtgatcat accaacgtgt tatacactca actagaanat aataagcttt aatctgaggg
                                                                       300
caagtacagt cctgacaaaa gggcaagttt gcataataga tcttcgatca attctctctc
                                                                       360
caaggggccc gcaactaggc tattattcat aaaacacaac tgaanagggg attggttta
                                                                      420
ctggtaaatc atgtgntgct aaatcatttt ctgaacagtg gggtctaaat cantcattga
                                                                       480
tttagtggca gccacctgcc cggcggccgn tcgaagccca attctgcaga tatccatcac
                                                                       540
actggcggcc g
                                                                       551
      <210> 143
      <211> 515
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(515)
     <223> n = A,T,C or G
      <400> 143
cgagnggccc gcccgggcag gtatcttcac aaactcaaca aaggcactac atgagacttc
                                                                       60
```

```
acattcccct agtccaatag ctgacaaatt tttgcaacgt tctgcaatgc gaattaactc
                                                                        120
 ttcatcaagt ggccgtaatc catttgcaca cactactagt tcaaccagtc tagggcatgt.
                                                                        180
 catteccaca eggecaagea catetteget tactgatete ecaaagtaca gatgggtgge
                                                                        240
 aggtatttca tagcgaaaga aggggtcaaa ttcttcttca tataanaaaa aatacatcac
                                                                        300
 taagttcact ttgggtgaat gtctgatgaa agcatcccag ctactcttct gaatagtatg
                                                                        360
 gaagtgtgtc tgtccaggat tctcactgac tacatcaatg cgcaaatgtt ctaatcgaac
                                                                        420
 atgtttttca gaagacaatg caagtaacaa ctcatcacte aataagtggt aagttcaggg
                                                                        480
 ctagttctct taagccgnga cactgatcag cacac
                                                                        515
       <210> 144
       <211> 247
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(247)
      <223> n = A,T,C or G
      <400> 144
tgcattctct ntggatgcan acctgcccgt tggtagggac tntgctcaca cggaacatgg
                                                                         60
acggttacac ctgtgccgtg ggtgacgtcc accagcttct ggatcatctc ggcgngggtg
                                                                        120
ttgtggaagg gcagactatc cacctccatg cncacgatgc ccganacgcc actccggact
                                                                        180
ntgtgctgca ccaanatgcc cagcattnta tcttcaagca nagcacttat cagggtcctt
                                                                        240
ggcacac
                                                                        247
      <210> 145
      <211> 309
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (309)
      <223> n = A, T, C or G
      <400> 145
cgtgggtcgc ggcccgangt ctgctgtaac aaaacaccat agtctgggca gctcatagac
                                                                        60
aatggaattt tattteteac gettetggag getggattee aagateaagg tteeaggaga
                                                                       120
ctcagtgtct ggcaaggtct cggtttctgc ctcanagatg gtgccatctg gctgtgtcct
                                                                       180
cacaagtagg aaggtgcaag aagctcccct caggctctgt ctgtaagaca ctgatcccat
                                                                       240
tcatganggg gaaacgtaat gacctaatca gccccagag accccacttc taacaccatc
                                                                       300
accttgggg
                                                                       309
      <210> 146
      <211> 486
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(486)
      <223> n = A,T,C or G
      <400> 146
```

```
agcgtgggtc gcggcncgac gtcctgtcca tatttcacag cccgagaact aatacaagat
                                                                         60
gctgacatca tattttgtcc ctacaactat cttctanatg cacaaataag ggaaagtatg
                                                                        120
gatttaaatc tgaaagaaca ggttgtcatt ttanatgaag ctcataacat cgaggactgt
                                                                        180
gctcgggaat cagcaagtta cagtgtaaca gaagttcagc ttcggtttgc tcgggatgaa
                                                                        240
ctanatagta tggtcaacaa taatataagg aaganagatc atgaacccct acgagctgtg
                                                                        300
tgctgtagcc tcattaattg gntagaagca aacgctgaat atcttgnana angagantat
                                                                        360
gaatcagett gtaaaatatg gagtggaaat gaaatgetet taaetttaca caaaatgggt
                                                                        420
atcaccactg ctacttttcc cattttgcng gtaagatatn ttttctacct gngaaacgta
                                                                        480
tttaaq
                                                                        486
      <210> 147
      <211> 430
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(430)
      \langle 223 \rangle n = A,T,C or G
      <400> 147
gccgcccggg cangttcgac attacninga gttccatgat gtacaattct ttcacqaaaa
                                                                        60
acaatgaatg caagaatttg aggatctcct tactcctccc ttttacagat ggtctctcaa
                                                                        120
tecettette tteetettea tetteatett ettetgaacg egetgeeggg taceaegget
                                                                        180
ttctttgtct ttatcgtgag atgaaggtga tgcttctgtt tcttctacca taactgaaga
                                                                        240
aatttegetg caagtetett gactggetgt tteteegact tegeettint gteaaaegng
                                                                        300
agtettttta ceteatgece eteagettea eageatette atetggatgt thatttetea
                                                                       360
aagggeteae tgaggaaaet tetgattean atgtegaana geaetgtgaa gttttetett
                                                                       420
cattttgctg
                                                                       430
      <210> 148
      <211> 483
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(483)
      <223> n = A, T, C or G
      <400> 148
cccgggcagg tctgtgttgn tttncaaccg gtgtcctccc cagcgtccag aananggaaa
                                                                        60
tgtggagcgg gtgatgatga cocctegetg teetgteace teetgeacag ettegtatgt
                                                                       120
gggtctggtc tgggaccacc cgtacaggtt gtgcacgttg tagtgctcca cgggggagct
                                                                       180
gtccggcagg atctgctgac tctccatgca cagagtcttg ctgctcaggc ccttgtccct
                                                                       240
agattccaaa tatggcatat agggtggggt tatttagcat ttcattgctg cagccctga
                                                                       300
cagatccatc cacaaaattt gatggctcat tcatatcaat ccacaatcca tcaaacttca
                                                                       360
agetettete tggntetega nggtttgeat agaactette tatetette ttecaceaeg
                                                                       420
canacetegg negegaceae getaageega attetgeana tateeateae aetggeggee
                                                                       480
gct
                                                                       483
     <210> 149
     <211> 439
     <212> DNA
     <213> Homo sapien
```

```
<220>
       <221> misc_feature
       <222> (1)...(439)
       <223> n = A, T, C or G
       <400> 149
 ctttcacgaa nacaatgaat gcaagaattt gaggatctcc ttactcctcc cttttacaga
                                                                         60
 tggtctctca atcccttctt cttcctcttc atcttcatct tcttctgaac gcgctgccqq
                                                                        120
 gtaccacggc tttctttgtc tttatcgtga gatgaaggtg atgcttctgt ttcttctacc
                                                                        180
 ataactgaag aaatttcgct gcaagtctct tgactggctg tttctccgac ttcgcctttt
                                                                        240
 tgcaaacgtg agtctttta cctcatgccc ctcagcttcc acagcatctt catctggatg
                                                                        300
 ttcatttctc aaagggctca ctgaggaaac ttctgactca catgtcgaag aagcactgng
                                                                        360
agtttctctt catttgctgc aaanttgctc tttgctggct gngctctcag accacccatt
                                                                        420
tggctgcatg ggggctgac
                                                                        439
       <210> 150
       <211> 578
       <212> DNA
       <213> Homo sapien
       <220>
      <221> misc_feature
       <222> (1)...(578)
      <223> n = A,T,C or G
      <400> 150
ggcncgcccg ggcangtcca ctccactttt gagctctgag ggaatacctt caggagggac
                                                                         60
agggtcaggg agtcctggca gctccgcagc agagattcac attcattcag agacttgttg
                                                                        120
tccagtgcaa tgccattgat cgcaacgatc ctgtctccca cagcaaggga cccttcttta
                                                                        180
gcggcagggc ttccaggcag cacageggca gcatacactc cattctccag actgatgcca
                                                                       240
ctgtctttct gtccactgan gttgatgtgc agcggcgtga ccaccttccc acccagggac
                                                                       300
ttcctccgcc gcacgaccat gttgatgggc cccctnccca ttgaggagcg ccttgatggc
                                                                       360
ctgcttcttg nccttggtga tgaagtccac atcggtgatt ctcacagcca gtcattgacc
                                                                       420
cttaagcggn catcagcaat gcttcctttg gccactttag ngacaaatat gccacagtcc
                                                                       480
ccgggaaaca agggtcattc acaccttctg gcatatcaaa cacctcggcc gggancacta
                                                                       540
agccgaattc tgcagatatc catcacactg gngggccg
                                                                       578
      <210> 151
      <211> 503
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(503)
      <223> n = A, T, C or G
      <400> 151
cgagcggccc gcccgggcag gtctgggaga tcagcgactg ctgccacgtg cccagaaatg
                                                                        60
getegteett teactacage ggaatgeaat gagggtgggt gagaagatga tgggteggtt
                                                                       120
atttcattcc ttttcttttt acaacttcac tttcagagac ttcagcgttc catgtctgct
                                                                       180
gtgctgtgga acccagagtg ctcttgcctg gatggctgag aatcccttgg accctggaag
                                                                       240
cacctactcc atgatggccc ggtatagtgc aggetcaata taatetteec ggtatettga
                                                                       300
gttgataact cgttgccgtt tcttttcttg cttaacctct ttctctgtga aaatctcatt
                                                                       360
```

```
gaagegeatg tetgaageta etgaeagtet anatttgaet etettgggaa getetteate
                                                                        420
cagtgtgtat acatcatctc tcttaaccac aagttggagc catncttaaa cttcacctgg
                                                                        480
 tacatttgga tagggtggga ggc
                                                                        503
       <210> 152
       <211> 553
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(553)
       <223> n = A,T,C or G
       <400> 152
agcgtggtcg cggcccgagg tccactgagc tccgccttcc ccgggctccc tgaggaagca
                                                                         60
gagtcctgac ttccaggaag gacaggacac agaggcaaga actcagcctg tgaggctctq
                                                                        120
ggtggctcct gaggccagag gacgccttcc gcgatccatg gctcagcatc gtccttctgg
                                                                        180
cttcccagcc ccgggccgaa cgttcgggtt aataagcaga gcagttattc ggctcctggc
                                                                        240
aggagetece cegttagttt ceaegttgtg ageacattea taettaagae tgnttetett
                                                                        300
tgtgttttaa gcgtctgtct ctgtagtaaa ctgaaatgtt aacagaaatg cagacctgcc
                                                                        360
cgggcggccg ctcgaaagcc gaattctgca gatatccatc acactggcgg ccgctcgagc
                                                                        420
atgcatctag anggcccaat tcgccctata gtgagtcgna ttacaattca ctgggccgcg
                                                                        480
ntttacaacg tcgtgactgg gaaaaccctg cggtacccac ttaatcgcct tgcagnacat
                                                                        540
cccctttcg cca
                                                                        553
      <210> 153
      <211> 454
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(454)
      <223> n = A, T, C \text{ or } G
      <400> 153
togagogget ogcoogggea ggtocaccta gcatggetoc totaaacacg caactcagog
                                                                       - 60
aggggacccc cttcacctct ggcaagagag ctgggtagat cagaaacttg gtgacacctg
                                                                       120
gctagcacag agcaggetca cttgtcttgg tcccactacc cagattcctg cagacattgc
                                                                       180
aaaccaaatg aaggitgnig aatgacccct giccccagcc actigititg giatcatcig
                                                                       240
ctctgcagtg gaatgcctgt gtgtttgagt tcactctgca tctgtatatt tgagtataga
                                                                       300
aaccgantca agtgatctgt gcatncagac acactggggc acctgancac agaacaaatc
                                                                       360
accttaacga tctggaatga aactgnganc antgcccgcc tgggtgggtc tgganaaact
                                                                       420
gccgncttct tgttggacct tggccgcacc acct
                                                                       454
      <210> 154
      <211> 596
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(596)
     <223> n = A,T,C or G
```

```
<400> 154
 agcgtggtcg cggcccgang gcggcctcct gantganggg aagggacgtg ggggcggcca
                                                                         60
 cggcaggatt aacctccatt tcagctaatc atgggagaga ttaaagtctc tcctgattat
                                                                        120
 aactggttta naggtacagt tccccttaaa aagattattg tggatgatga tgacagtaag
                                                                        180
 atatggtcgc tctatgacgc gggcccccga agtatcaggt gtcctctcat attcctgccc
                                                                       240
 cctgtcagtg gaactgcaga tgtcttttc cggcagattt tggctctgac tggatgggt
                                                                        300
 taccgggtta tcgctttgca gtatccagtt tattgggacc atctcgagtt cttgtgatgg
                                                                       360
 attcacaaaa cttttanacc atttacaatt ggataaagtt catcttttg gcgcttcttt
                                                                       420
 gggangettt ttggeecana aatttgetga atacaeteae aaateteeta gaageeatte
                                                                       480
 cctaatcctc tgcaattcct tcagngacac ctctatcttc aaccaacttg gactggaaac
                                                                       540
 agetttgget gatgeetgea tttatgetea aaaaatagtt ettggaaatt tteate
                                                                       596
      <210> 155
      <211> 343
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(343)
      <223> n = A,T,C or G
      <400> 155
ctcganttgg cncgcccggg cangtctgcc tggtttttga ccgngcgagc tatttagnct
                                                                        60
ctggctctgt ttccggagct caaggnaaaa atcttgaana actcgagcag cttctgtgga
                                                                       120
tagccttggg tacacatact gccgagcata gccaatgtac tttctcaata gctggtgggg
                                                                       180
aatgggatct attgtttctc caggaaccac ctttagtctt tctgataatg gcttctcaga
                                                                       240
aactacttca agtacggaag tatttgaatc ttgactatnc atacgagcta ctgtggcact
                                                                       300
gctaatgggn tctctgctnt ccagctctta ttgcaatcac atg
                                                                       343
      <210> 156
      <211> 556
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(556)
      <223> n = A,T,C or G
      <400> 156
tcgagcggcc cgcccgggca ggtctggcac cacncagatc gattaactgg ctcatctgat
                                                                        60
ctcgtggccc ccaccctgga actgacttag cacaaaagga cacctcaatt ccttatgatt
                                                                       120
tcatctccga cccaaccaat caacaccctt gactcactgg ccttccccct cccaccaaat
                                                                       180
tateettaaa aactetgate eeegaatget eagggagate gatttgagta etaataagae
                                                                       240
tecagtetee tgcacaagea getetgtgta etetteetet attgcaatte etgtettgat
                                                                       300
aaatcggctc tgtgtaggcg gcggaagaag tgaacctgtt gggcggttac cacctctgtc
                                                                       360
gtgtgtgaca gttgntttga atctctaatt gctcagtaca gatccacatg caggttaagt
                                                                       420
aagaagcttt tgaagaaaat ggaaagtctt aagtgatggc ttccaagaaa tcaaacctac
                                                                       480
attaattagg gaacaacgga ctttacgtat cacaaatgaa gagactgacn aagtaaatca
                                                                       540
acttggcctt ttctta
                                                                       556
```

<210> 157
<211> 333

```
<212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (333)
       \langle 223 \rangle n = A,T,C or G
       <400> 157
 ggtccacaaa aatatatnaa ataagctgga tatataaaan caaacactta acatngncan
                                                                         60
 catteettea gttatteaaa eteaetgata netaaenggg agnagttggn attetggaag
                                                                        120
acttectaag etaaaagtat atttacatat ttacaacaca ngtaaatata aengaagaac
                                                                        180
tacttcaaat aangnngaaa ttccagaatt ctanagattt atagctatag ntnacaanta
                                                                        240
tcaccaattg gtttgcaatc aanngnccag cactacttat gannaangtt taactannaa
                                                                        300
accaaaaggg gagaaaacct ggnagggaaa nat
                                                                        333
      <210> 158
      <211> 629
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(629)
      <223> n = A, T, C or G
      <400> 158
togagoggoo geoogggoag gtotggtaca tttgtgcgag gtocggoact ctgttctcat
                                                                         60
ccagtaagtg gtcgagccct ttctgcagaa ttgctgttaa atgttctcct aatagctgtt
                                                                        120
tctccacaca agcaatcagt ggtttctgtg tgctgtggtc caagtaagtg attactctgt
ctccctcttc ttctaagcgt ttacttacat ggttaagata ttctggaacc tctctttcct
                                                                        240
gcattaacct ttggccttcg gcagcatata agcaattagt ctcttccaaa aatttcagtt
                                                                        300
caaatgaatc tttatacacc tgcaggtcag acagcatgcc caggnaggct ccgcaacagg
                                                                        360
ctccggtcca cggcctcgcc gctcctctcg cgctcgatca gcagtaggat tccatcaatg
                                                                        420
gttttactct gaaccatttt atcactaata atatgggttc taaacagttc taatcccata
                                                                        480
tcccagatgg agggcagcgt ggagttctgc agcacatagg tgcggtccaa gaacaggaag
                                                                        540
atgettetga teatgaatea tttgnetgge aatggteetg ceageacgtg gtaatettte
                                                                        600
ttttaaaaat aaacccttat ctaaacgtc
                                                                        629
      <210> 159
      <211> 629
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(629)
      <223> n = A, T, C or G
     <400> 159
tcgagcggcc gcccgggcag gttctagagg ganaatctgg ctgatttggg aataaaatat
                                                                        60
aatcgaatat tcaacaccat gaagataaat cttattttgg aaatctactg accttaatac
                                                                       120
cccaagettg ccctgaatac tttgattgga attggaatat atcaaaaaag gttagtattt
                                                                       180
ttgttgtagt taggatacta aaaggatatt agttacccaa gagatccaat ttgtttttct
                                                                       240
gatgaatagt gttcagtaaa atgaagcagt cttaagagtg actaataatt tcaaagtgat
                                                                       300
```

```
ttttcgtcta ttcttaatat tttttaatta tttatttta agagttttat accttgagca
                                                                        360
 gatacaatga tccgctttag tgagaggaca atttctgatt gattgttttc tcttcaggcc
                                                                        420
 atctcacctc ttcattctct tgttacattt gaagcagttg atataatggg tttatacttt
                                                                        480
 aaaagataga catggtgcca tgaagtttgg ggaagttggg tgaattatcc cattctagtt
                                                                        540
 acagangage tttccttaaa tgccctttac ttctangttt ggtcaagaag tcatttctg
                                                                        600
 agtaaaagtt attttcatat atgttgggg
                                                                        629
       <210> 160
       <211> 519
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(519)
       <223> n = A, T, C or G
      <400> 160
tcgagcggcg cgcccgggca ggtctgctgg gattaatgcc aagttnttca gccataaggt
                                                                         60
agcgaaatct agcagaatcc agattacatc cacttccaat cacgcggtgt ttgggtaatc
                                                                       120
cacttagttt ccagataaca tacgtaagaa tgtccactgg gttggaaacc acaattatga
                                                                       180
tgcaatcagg actgtacttg acgatctgag gaataatgaa tttgaagaca ttaacatttc
                                                                       240
totgcaccag attgagooga ototocoott ottgotgacg gactootgca gttaccacta
                                                                       300
caatcttana attgggcggg tcacagaata atctttatct gccacaattt taggtgctga
                                                                       360
agaaataagc tcccatgctg cagatccatc atttctnctt taagcttatc ttccaaaaca
                                                                       420
tccacaagan caangttcat cagccagaga ctttcccaga atgctgatag nacacgccat
                                                                       480
accaacttgt ccaacancca ctacagcgat cttattggt
                                                                       519
      <210> 161
      <211> 446
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(446)
      <223> n = A,T,C or G
      <400> 161
cgagnggccc gcccgggcag gtccagtaag cntttnacga tgatgggaaa ggttatgcaa
                                                                        60
ggtcccagcg gtacaacgag ctgtttctac atcatttgta ttctgcatgg tacgtacaat
                                                                       120
agcagacacc atctgaggag aacgcatgat agcgtgtctg gaagcttcct ttttagaaag
                                                                       180
ctgatggacc ataactgcag ccttattaac caccacctgg tcctcgtcat ttagcagttt
                                                                       240
tgtcagttca gggattgcac gtgtggcang ttctgcatca tcttgatagt taatcaagtt
                                                                       300
tacaactggc atgtttcagc atctgcgatg ggctcagcaa acgctggaca ttantgggat
                                                                       360
gagcagcatc aaactgtgta natgggatct gcatgccctc atctaatgtc tcagggaaca
                                                                       420
tagcageteg taccetetga getega
                                                                       446
      <210> 162
      <211> 354
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc feature
```

```
<222> (1)...(354)
       <223> n = A, T, C or G
       <400> 162
 agegringteg eggeeegang teetgggaag certinitge tgageeteae ageetetgte
                                                                         60
 aggeggetge ggatecageg gtecaceagg eteteatgge eteegggetg ggaggngggt
                                                                        120
 gagggcacaa aaccetteee aaggecacga anggeaaact tggtggcatt ccanagettg
                                                                        180
 ttgcanaagt ggcggnaacc cagtatccgg ttcacatcca ggntgatgtc acgacctgg
                                                                        240
gacatgtang cacataatcc aaaccggaga gcatcggtgc cacattcacg aatccccgct
                                                                        300
gggaagtcag ctttctgccc ttctttggcc ttctccacct cgctgggatc cagg
                                                                        354
       <210> 163
       <211> 258
       <212> DNA
     <213> Homo sapien
       <220>
       <221> misc_feature
      <222> (1)...(258)
      <223> n = A,T,C or G
      <400> 163
tttttcncca agtcctcttg ccgngggatc tngactgcaa tttaagacac ttctaattag
                                                                         60
ttatacccag gccctgcaaa attgctgggt ttatataata tattcttgct gcacgaagat
                                                                        120
ttattattct gttggatgat tctattttaa ttntatttat tctggccaaa aaagaacctt
                                                                        180
ctccgctcgt caagagangc caatntgtct tgaaggacaa gagaaagatg ctaacacaca
                                                                        240
ctttcttctt cttgagga
                                                                        258
      <210> 164
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(282)
      <223> n = A,T,C or G
      <400> 164
ggaacatatt acttttaaat tacttgggtc aatgaaacat ttaataaaaa catttgcttc
                                                                        60
tctatataat acgtatgtat aaaataagcc ttttcanaaa ctctggttct cataatcctc
                                                                       120
tataaatcan atgatctgac ttctaagagg aacaaattac agnaaggggt atacattnat
                                                                       180
gaatactggt agtactagag ganngacgct aaaccactct actaccactt gcggaactct
                                                                       240
cacagggtaa atgacaaagc caatgactga ctctaaaaac aa
                                                                       282
      <210> 165
      <211> 462
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(462)
     <223> n = A,T,C \text{ or } G
```

```
<400> 165
gcccgggcan gtcctgtaat cccagctact cangangctg agtcatgana atcgcctgaa
                                                                         60
tccgggaggt agaggccgca gcgagcaaag attaagccac tgcactccag tctgggtgac
                                                                        120
agagtgagaa tetgtetgtt geteetetgg cattggtetg aaatgggttt gtagaacatg
                                                                        180
ccacagaagg accagcanca gcaacaaatg gatttgtgga angcgtagct ccaaatggag
                                                                        240
cangeacact tgatgaagea egetgtgtet gtgeagange aaceaetgge aetgtteeaa
                                                                        300
aaacattgct gctagcatta cttgtggaag tatacgcatt actggaggtg gctgcanaac
                                                                        360
tgaaaacgct gtctagttct gccanagctg catacttgnc tgaanatgca cttgactgac
                                                                        420
tgggaactga accacanaac caacaggacc tttacctgtg ga
                                                                        462
      <210> 166
      <211> 365
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(365)
      <223> n = A,T,C \text{ or } G
      <400> 166
cgtgggtcgc ggcncgangt ctgaaaccaa tccagaacta aacatcagca cacaaaaaat
                                                                        60
accaggatag atggaatcaa aagactctga agccaaaagg aggctaggga gagcaactga
                                                                        120
acttagcaag ctgaggactt cagtgtccat catccgatcc tgccctgtaa caacaggtct
                                                                       180
atatgataga gatattecat etgagetgga ggecattate ettageaaac taacacagaa
                                                                       240
cagaaaacca aatacatgtt ctcatttaga agtaggagct aaatgatgag aactcaagga
                                                                       300
cacaaagaaa ggaacaacag acactggggc ctacttgagg gtggagggtg ggaggaggga
                                                                       360
gaaga
                                                                       365
      <210> 167
      <211> 364
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(364)
      <223> n = A, T, C or G
      <400> 167
agcgtggtcg cggcgcgang tccagcccta gcttgcctgt gactccgcct tcactgggtg
                                                                        60
ctctctctaa aagttgctga ctctttactg tatctcccaa ttcccactcc attggttcca
                                                                       120
taaggggagg ggtgtctcac tcaacatggt gttcctggta ccaagaactg gctgacgaag
                                                                       180
ctgggtgccg tggctcatgc ctgtaatccc agcacttttg ggaggccaag aagggcgat
                                                                       240
cacctgaggt ctggagttca agatcagcct gaccaacatg atgaaaccaa gtctccacta
                                                                       300
aaaatataaa acaattagcc aggcatggtg gtgggtgcct gnaatcccag ctactgggga
                                                                       360
ngct
                                                                       364
     <210> 168
      <211> 447
     <212> DNA
     <213> Homo sapien
     <220>
     <221> misc_feature
```

```
<222> (1)...(447)
       <223> n = A, T, C \text{ or } G
       <400> 168
 cccgggcagg tcaaaaccca aaacctttca ttttagccca aaccagctca tgattaggta
                                                                         60
 tacaaggata acagaaccag ttgtcaggac gagcatttga caagtaaaag caattcttgc
                                                                        120
 aaagctgcag ttcatccagc tcatggcatg tgtctttata tagcatcctc gcaatgtcag
                                                                        180
 cttgctcact gtctgctcca tagaaaatca cggtattgtg gagaagcaat tgggcatcag
                                                                        240
 ctttgaactc ttcataactt cggtatttcc cttcattcac tttctcttga atggtgggaa
                                                                        300
 cgtccacaga cctcggccgc gaccacgcta agcccgaatt ctgcagatat ccatcacact
                                                                        360
 ggcggccgtt cgagcatggc atctagaagg cccaattcgc ctatagngag tcgnattacc
                                                                        420
 aattcactgg ccgtcgnttt acaacgc
                                                                        447
       <210> 169
       <211> 524
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(524)
       <223> n = A,T,C or G
      <400> 169
cgantngcgc gcccgggcag gtctgagcag cctttctgnn tgctggacta ttgggattgg
                                                                         60
gttcatccaa cagagactgt atggatgtta gaatggaaga cacatcatag gttggactcc
                                                                        120
aacggttctg aagtatgtcc agacatatac taccatctgc atagactaag aacaaagaag
                                                                        180
taggtacatt aaacgtaaca agaccactaa ggttttaaca ttatagacaa aacanaaata
                                                                        240
gtcaaganta ctttgctttt gaagtttaaa gattcctatg ttgcttccca gttaactgcc
                                                                        300
taaaaagata agncataacc accactagtg aaataatcan gatgatcaga gaatgtcana
                                                                        360
tgtgatcagt ataaaactgg angatattna gtgtcatcct ttggaaaagg ctgccctatn
                                                                        420
atccaggaaa tcanaaacat tnttgaacag ggnccctagc tatccacaga catgtgggaa
                                                                        480
attcattccc caaatngtag gctggatccc ctatctgaaa taac
                                                                        524
      <210> 170
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(332)
      <223> n = A, T, C or G
      <400> 170
teganeggen egecegggea ggtgacaaac etgttattga agatgttggt tetgatgagg
                                                                        60
aanaanatca gaagggatgg tgacaagaan aanaanaaga agattaagga aaagtacatc
                                                                       120
gatcaagaag agctcaacaa aacaaagccc atctggacca gaaatcccga cgatattact
                                                                       180
aatgangagt acggagaatt ctataanagc ttgaccaatg actgggaaga tcacttggca
                                                                       240
gtgaagcatt tttcagttga nggacagttg gaattcagag cccttctatn tgtcccacga
                                                                       300
cgtgctcctt ttgatctgtt tganancaga aa
                                                                       332
      <210> 171
      <211> 334
      <212> DNA
```

```
<213> Homo sapien .
       <220>
       <221> misc feature
       <222> (1)...(334)
       <223> n = A,T,C or G
       <400> 171
 cgagnggcnc gcccgggcag gtctgttgat agcgacttaa cagaaaagtc tagacaaaca
                                                                         60
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tggagtgcag tggcgcggat tacagctcac tggagtcttg acttcccagg cacaagcaat
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      <221> misc_feature
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cataccaggt agtaagntcg tctaggctga tgtttacacc tggggtcaga ccaagtanga
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                                                                     1080
graattccag tgtttgtcac gtggttgttg aataaatgaa taaagaatga gaaaaccaga
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<213> Homo sapien

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<213> Artificial Sequence

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<223> Made in the Lab

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<210> 178

<211> 1665

<212> DNA <213> Homo sapien

<400> 178

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                                                                    240
gaaatggata aaataagtgg aaaattagaa gattcaacta gcctatcaaa aatcttggat
                                                                    300
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                                                                    600
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                                                                   1500
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<211> 179

<212> PRT

<213> Homo sapien

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Val Leu Lys Lys Lys Leu Ser Glu Ala Lys Glu Ile Lys Ser Gln Leu Glu Asn Gln Lys Val Lys Trp Glu Gln Glu Leu Cys Ser Val Arg Leu 55 Thr Leu Asn Gln Glu Glu Lys Arg Arg Asn Ala Asp Ile Leu Asn 70 Glu Lys Ile Arg Glu Glu Leu Gly Arg Ile Glu Glu Gln His Arg Lys Glu Leu Glu Val Lys Gln Gln Leu Glu Gln Ala Leu Arg Ile Gln Asp 105 Ile Glu Leu Lys Ser Val Glu Ser Asn Leu Asn Gln Val Ser His Thr . 120 His Glu Asn Glu Asn Tyr Leu Leu His Glu Asn Cys Met Leu Lys Lys 135 140 Glu Ile Ala Met Leu Lys Leu Glu Ile Ala Thr Leu Lys His Gln Tyr 150 155 Gln Glu Lys Glu Asn Lys Tyr Phe Glu Asp Ile Lys Ile Leu Lys Glu 165 170 Lys Asn Ala Glu Leu Gln Met Thr Leu Lys Leu Lys Glu Glu Ser Leu 180 185 Thr Lys Arg Ala Ser Gln Tyr Ser Gly Gln Leu Lys Val Leu Ile Ala 200 Glu Asn Thr Met Leu Thr Ser Lys Leu Lys Glu Lys Gln Asp Lys Glu 215 Ile Leu Glu Ala Glu Ile Glu Ser His His Pro Arg Leu Ala Ser Ala 230 235 Val Gln Asp His Asp Gln Ile Val Thr Ser Arg Lys Ser Gln Glu Pro 245 250 Ala Phe His Ile Ala Gly Asp Ala Cys Leu Gln Arg Lys Met Asn Val ¹ 260 265 Asp Val Ser Ser Thr Ile Tyr Asn Asn Glu Val Leu His Gln Pro Leu 280 Ser Glu Ala Gln Arg Lys Ser Lys Ser Leu Lys Ile Asn Leu Asn Tyr 295 300. Ala Gly Asp Ala Leu Arg Glu Asn Thr Leu Val Ser Glu His Ala Gln 310 315 Arg Asp Gln Arg Glu Thr Gln Cys Gln Met Lys Glu Ala Glu His Met 325 330 Tyr Gln Asn Glu Gln Asp Asn Val Asn Lys His Thr Glu Gln Glu 345 Ser Leu Asp Gln Lys Leu Phe Gln Leu Gln Ser Lys Asn Met Trp Leu 355 360 Gln Gln Gln Leu Val His Ala His Lys Lys Ala Asp Asn Lys Ser Lys 370 375 Ile Thr Ile Asp Ile His Phe Leu Glu Arg Lys Met Gln His His Leu 390 395 Leu Lys Glu Lys Asn Glu Glu Ile Phe Asn Tyr Asn Asn His Leu Lys 405 Asn Arg Ile Tyr Gln Tyr Glu Lys Glu Lys Ala Glu Thr Glu Asn Ser

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<211> 511

<212> DNA

<213> Homo sapiens

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gccaggtgca gcgtccatct ccacattgac atctccaccc acctggcctc tcagggcatt 180
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 <213> Homo sapiens
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gatgttgagc tttttcgcgt tgacaaaatc aaacagtttc ccgtactcct ccctctcaat 360
gctgctgaag gtatactgag tgccctgctt ggtctcaatt tcaaagtcaa aggaacgagt 420
agtagtggta ccacgagcaa agttgacaaa ggagatctca tcgaagcgga tgtgcacagg 480
tggcttgtgg acgtagatga a
<210> 191
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (49)
<223> n=A,T,C or G
<400> 191
ggaaaaactg tgaaaaatat atctgaattt attaagtaca gtataaaana gggttgtggc 60
aacagaaagt aaaaactaac atggattgct ataaatatgc tgaagcctag ttgttcaaat 120
gatacaattc tctcatgcta ctctaaagtt tataaagaaa aaggatttac actttacaca 180
ctgtacacaa aaggaatacc ttctgagagc cagggagtgg ggaaagggga aggagacttg 240
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<210> 192
<211> 271
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(271)
<223> n=A,T,C or G
<400> 192
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gatagaagan caaaccacgt cccacgaatc ccaataatga cagcttcaga ctttgctttt 120
ttaacaattt gaaaaattat totttaatgt ataaagtaat tttatgtaaa ttaataaatc 180
ataatttcat ttccacattg attaaagctg ctgtatagat ttagggngca ggacttaata 240
atagnggaaa tgaaattatg atttattaat c
                                                                  271
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<211> 351
 <212> DNA
 <213> Homo sapiens
 <400> 193
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 gaccaccgtt cagtcatttt gggttgccgt gctcccaaaa cattttaaat gaaagtattg 180
 gcattcaaaa agacagcaga caaaatgaaa gaaaatgaga gcagaaagta agcatttcca 240
 gcctatctaa tttctttagt tttctatttg cctccagtgc agtccatttc ctaatgtata 300
 ccagcctact gtactattta aaatgctcaa tttcagcacc gatggacctg c 360
 <210> 194
 <211> 311
 <212> DNA
 <213> Homo sapiens
 <400> 194
ctgagacaca gaggcccact gcgagggga cagtggcggt gggactgacc tgctgacagt 60
caccetecet etgetgggat gaggteeagg agecaactaa aacaatggea gaggagacat 120
ctctggtgtt cccaccaccc tagatgaaaa tccacagcac agacctctac cgtgtttctc 180
 ttccatccct aaaccacttc cttaaaatgt ttggatttgc aaagccaatt tggggcctgt 240
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 tgacacagac c
 <210> 195
 <211> 381
 <212> DNA
 <213> Homo sapiens
<400> 195
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gccaacagga tgacatgaaa tgatgtactc agaagtgtcc tggaatgggg cccatgagat 120
ggttgtctga gagagagctt cttgtcctgt ctttttcctt ccaatcaggg gctcgctctt 180
ctgattattc ttcagggcaa tgacataaat tgtatattcg gttcccggtt ccaggccagt 240
aatagtagcc tetgtgacae cagggegggg eegagggace aettetetgg gaggagacee 300
aggettetea taettgatga tgtageeggt aateetggea egtggegget geeatgatae 360
cagcagggaa ttgggtgtgg t
                                                                   381
<210> 196
<211> 401
<212> DNA
<213> Homo sapiens
<400> 196
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gcccaaacct ggagacctga ttgagatttt ccgccttggc tatgagcact gggccctgta 120
tataggagat ggctacgtga tccatctggc tcctccaagt gagtaccccg gggctggctc 180
ctccagtgtc ttctcagtcc tgagcaacag tgcagaggtg aaacgggagc gcctggaaga 240
tgtggtggga ggctgttgct atcgggtcaa caacagcttg gaccatgagt accaaccacg 300
gcccgtggag gtgatcacca gttctgcgaa ggagatggtt ggtcagaaga tgaagtacag 360
tattgtgagc aggaactgtg agcactttgt cacccagacc t
<210> 197
<211> 471
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<212> DNA
 <213> Homo sapiens
 <400> 197
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 aactttgtac cttgattgcc ttacaaagtt atttgtttac aaacagcgac catataaaag 120
 cctcctgccc caaagcttgt gggcacatgg gcacatacag actcacatac agacacacac 180
 atatatgtac agacatgtac tctcacacac acaggcacca gcatacacac gtttttctag 240
 gtacagetee caggaacage taggtgggaa agteecatea etgagggage etaaccatgt 300
 ccctgaacaa aaattgggca ctcatctatt ccttttctct tgtgtcccta ctcattgaaa 360
 ccaaactctg gaaaggaccc aatgtaccag tatttatacc tctagtgaag cacagagaga 420
 ggaagagagc tgcttaaact cacacaacaa tgaactgcag acacagacct g 480
 <210> 198
 <211> 201
 <212> DNA
 <213> Homo sapiens
 <400> 198 .
 ggtccattga ggctctgtcg gccatgccca cagttcgaag ctttgccaac gaggagggcg 60
aagcccagaa gtttagggaa aagctgcaag aaataaagac actcaaccag aaggaggctg 120
 tggcctatgc agtcaactcc tggaccacta gtatttcagg tatgctgctg aaagtgggaa 180
tcctctacat tggtgggcag a
                                                                    201
 <210> 199
 <211> 551
<212> DNA
<213> Homo sapiens
<400> 199
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gggcctggaa cacaccatct tccccatgag cccggtgccc agtctggtga cttccatctt 120
ggcccctggc cttatgtccc agttatgacc cctgacttca actctggctc.ttaccctgta 180
actccagtcc atctctgaca tttttaacac ccggccttgt gaccgtggac atagctcctg 240
acctcgattc ccatcttgag cccagtgtta gtccatgaga tcatgacctg actcctggtc 300
tccaaccttg tgatcctaat tctgggacct caatcctagc ctctgaactt gggaccctgg 360
agetectgae ettagteetg acegetacee ttgattetga cetttgatee tgtaacttag 420
gggtggcccc tgaccttatt actgtcattt agctccttga ccttgccact tcaatcctgg 480
ctttatgacc tcctactctc aattttaact ttaaccaaat gaccaaattt gtgacactaa 540
atgaccacaa t
<210> 200
<211>, 211
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(211)
<223> n=A,T,C or G
<400> 200
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tgtaagagag gctgctgnca ccattacctg cagaaacctt ctcatagggg ctacgatcgg 120
tactgctagg gggcacatag cgcccatggg tgtggtaggt ggggnactcn ntnataggat 180
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ggtaggtatc ccgggctgga aanatgnnca g
                                                                   211
 <210> 201
 <211> 111
 <212> DNA
 <213> Homo sapiens
 <400> 201
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 taatttccac actatttctc ccatattcct taaacttctt ggcatccacc t 120
<210> 202
<211> 331
<212> DNA
<213> Homo sapiens
<400> 202
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ggagagaga agagaggaaa attccctaac ccttggttta aagacaatat tcatttattg 120
ctcaaatgat gcttttaagg gaggacagtg gaataaaata aactttttt ttctccctac 180
aatacataga agggttatca aaccactcaa gtttcaaaat ctttccaggg tccaatatca 240
cttttttttt ttcggttcaa tgaaaagcta aatgtaataa tactaattat agataaaatt 300
ttattttact ttttaaaaat ttgtccagac c
<210> 203
<211> 491
<212> DNA
<213> Homo sapiens
<400> 203
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ggctttagtg taaccaataa arctgtagtg accttacctg tattccctgt gctatcctgt 120
gggaaggtag gaatgggcta agratgatga atgtataggt tagggatctt ttggttttaa 180
atcacagaaa acctaattca aactggctta aaataaaaag gatttattgg ttcatgtaac 240
tagaaagtcc ataggtagtg ctggctccag gtgaagactt gacccagtag ttcagtatgt 300
ctctaaatac cggactgact tttttctcac tgttgcatct tctgtaggac catttaagtc 360
tgggccactt aatggctgcc agcattccta agattacact tttccccatt tatgtccaat 420
cagaaaaaga aggcatcttt gtaccagaaa tctcagcaaa agccctaata ttcacactga 480
ttaggacctg c
<210> 204
<211> 361
<212> DNA
<213> Homo sapiens
<400> 204
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ttttcatttg atttttgtta agagtgcagt attgcagagt ctagaggaat ttttgtttcc 180
tigattaaca tgattiteet ggttgttaca tecagggeat ggeagtggee teageettaa 240
acttttgttc ctactcccac cctcagcgaa ctgggcagca cggggagggt ttggctaccc 300
ctgcccatcc ctgagccagg taccaccatt gtaaggaaac actttcagaa attcagacct 360
                                                                  361
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<211> 471
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (2)
<223> n=A,T,C or G
<221> misc feature
<222> (3)
<223> n=A,T,C or G
<400> 205
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ctctgaaacc agageteete eteceteece gggeagggtg gagetgagaa gggetgetet 120
agcgttggga ctccacctcc atacacctga tattttgata gggcaggtcc ctgctatggg 180
ccactgttct gggcagtata gtatgcttga cagcatcctt ggcatctatc caccagatcc 240
cagageacce getactaget gtgacaacat cetecaaaca ttgcaaaatt teeeetggga 300
ggcaagattg cctcagatgg gagaatcacg ctctagggaa atctgctggt atgagaaccc 360
caactececa etceaetgag cetecagatg gegageagge tgeageteca geaeagaeae 420
gaageteect ceagecactg aeggteeatg getggggtta ceeaggacet c 480
<210> 206
<211> 261
<212> DNA
<213> Homo sapiens
<400> 206
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tgtcctttct tcccaatcag agatttgtgg atgtgtggaa tgacaccacc accagcaatt 120
gtagccttga tgagagaatc caattcttca tctccacgaa tagcaagttg caagtgacga 180
ggggtaatac gctttacctt taagtctttt gatgcatttc ctgccagttc aagtacctct 240
gcggtgaggt actccaggat g
<210> 207
<211> 361
<212> DNA
<213> Homo sapiens
<400> 207
gctctccggg agcttgaaga agaaactggc tacaaagggg acattgccga atgttctcca 60
geggtetgta tggacceagg ettgteaaac tgtactatac acategtgac agteaceatt 120
aacggagatg atgccgaaaa cgcaaggccg aagccaaagc caggggatgg agagtttgtg 180
gaagtcattt ctttacccaa gaatgacctg ctgcagagac ttgatgctct ggtagctgaa 240
gaacatetea cagtggacge cagggtetat tectacgete tagcactgaa acatgcaaat 300
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<210> 208
<211> 381
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<222> (1)...(381)
 <223> n=A,T,C or G
 <400> 208
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 tagctaacta ataaagnttg atntaggcat tattatataa ttctgagtca ttcatggtat 180
 ctctcatgtt tgatgtattt tncaaactaa gatctatgat agtttttttt ccanagttcc 240
 attaaatcat ttatttcctt tactttctca cctctgtnga aacatttaga aactggattt 300
 gggaacccan ttttggaaaa ccagattcat agtcatgaaa atggaaactt ncatattctg 360
 tttttgaaaa gatgtggacc t
 <210> 209
 <211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (83)
<223> n=A,T,C or G
<400> 209
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tcagggtgtc attgaaagac agnggaaacc aggatgaaag tttttacatg tcacacacta 120
cattlcttca atatttcac caggacttcc gcaatgaggc ttcgtttctg aagggacatc 180
tgatccgtgc atctcttcac tcctaacttg gctgcaacag cttccacctg c 240
<210> 210
<211> 371
<212> DNA
<213> Homo sapiens
<400> 210
tccatcctgg ttttgcagag atcaggttgt tgacagttcc tggttgaccc acagctaccc 60
atgtcagtta tctccactaa catatccaag aatctttgta ggacaatttc tccacctgca 120
aggtttttta ggtagaactc ttcttttaag gcaattagcc cattgccaaa aggttttact 180
gtcttaaagc tgtctttctg agatctaatt ccaaggactt ctccacagct aagtgagatg 240
cctcacacca ttaggtgatg ctttggacag aacagagtat tttcatcttg tgtttaaagc 300
aatteettgg etteggetee teaceaettt etatgeeagt eteceattta tgteeetagt 360
aatgcctatg c
<210> 211
<211> 471
<212> DNA
<213> Homo sapiens
<400> 211
tttattttaa aagaaaaaaa ttaaaataga gccaacaaat gcaattaaga aaaaaaaagt 60
attgagacac aaggggacct acatgttctg gtctaagaag catgcaagta ttacaaaqca 120
ttccagatac agtatgacag aggaacagtg aacaagcatt ggaacgatgc tctttcttc 180
agaaacggga agtctaacag ttatgttttc acaatggtag tgattaaacc atcttattt 240
ttaaggaatt ttataggaag aattttagca ccatcattaa aggaaaaata ataatacctt 300
tttagccctg cctatctcca gtcttggaat aataacagaa gcatagcacc tttcagtatc 360
taaaatataa acaagaatag taagtccatc ccagcttcta gagatgaggt agctcatgct 420
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aagaaatgtt gggtcatttt tcctatgaaa gttcaaaggc caaatggtca c 480
 <210> 212
 <211> 401
 <212> DNA
 <213> Homo sapiens
 <400> 212
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 atattttggg ttcaaaaaaa gtaaaaagat aatgtagctg catttctttg gttattttgg 120
 gccccaaata tttcctcatc tttttgttgt tgtcatggat ggtggtgaca tggacttgtt 180
 tatagaggac aggtcagctc totggctcgg tgatctacat totgaagttg totgaaaatg 240
 tetteatgat taaatteage etaaaegttt tgeegggaae aetgeagaga caatgetgtg 300
 agtttccaac ctcagcccat ctgcgggcag agaaggtcta gtttgtccat caccattatg 360
atatcaggac tggttacttg gttaaggagg ggtctacctc g
                                                                    401
<210> 213
<211> 461
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(461)
<223> n=A,T,C or G
<400> 213
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ttccctaaga cctgaaaatg aacatagtat gctagttatt tttcagtgtt agccttttac 120
tttcctcaca caatttggaa tcatataata taggtacttt gtccctgatt aaataatgtg 180
acggatagaa tgcatcaagt gtttattatg aaaagagtgg aaaagtatat agcttttanc 240
aaaaggtgtt tgcccattct aagaaatgag cgaatatata gaaatagtgn gggcatttct 300
tcctgttagg tggagtgtat gtgttgacat ttctccccat ctcttcccac tctgtttnnt 360
ccccattatt tgaataaagt gactgctgaa nangactttg aatccttatc cacttaattt 420
aatgtttaaa gaaaaaccta taatggaaag tgagactcct t
                                                                   461
<210> 214
<211> 181
<212> DNA
<213> Homo sapiens
<400> 214
cctgagcttc tactcctttc ccttaagatt cctccaaagc accagctcca taaaatcctt 60
cagetececa gacecacace aagaaceeca catgitaatt ggateageea aatetacaag 120
cagataagtc ctaaggagaa tgccgaagcg tttttcttct tcctcaagcc tagcatgaga 180
                                                                   181
<210> 215
<211> 581
<212> DNA
<213> Homo sapiens
<400> 215
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ttatttaaat ctgcacctct ctctatttta tttgccaggg gcacgatgtg acatatctgc 120
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agtcccagca cagtgggaca aaaagaattt agaccccaaa agtgtcctcg gcatggatct 180
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 ttattcactt gttcattcaa gtatttattg aatacctgcc tcaagctaga gagaaaagag 300
 agtgcgcttt ggaaatttat tccagttttc agcctacagc agattatcag ctcggtgact 360
 tttctttctg ccaccattta ggtgatggtg tttgattcag agatggctga atttctattc 420
 ttagcttatt gtgactgttt cagatctagt ttgggaacag attagaggcc attgtcctct 480
 gtcctgatca ggtggcctgg ctgtttcttt ggatccctct gtcccagagc cacccagaac 540
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 <210> 216
 <211> 281
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(281)
 <223> n=A,T,C or G
 <400> 216
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 atccctagaa gtccaggagc tgtggggaag agaagcactt agggccagcc agccgggcac 120
ccccacttgc gccccgaccc acgctcacgc accagacctg cccnggcggt cgctcnaaag 180
ggcgaattct gcagatatcc atcacactgg cggacgctcg agcatgcatc tagagggccc 240
 aattcaccct atantgagtc gtattacaat tcactggccg t
 <210> 217
 <211> 356
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(356)
<223> n=A,T,C or G
<400> 217
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gtggtttgca gcaatccgta gttggtttct caccataccc tgcagttctg tgagccaaag 120
gtcttgcaga aagttaaaat aaatcacaaa gactgctgtc atatattaat tgcataaaca 180
cctcaacatt gctcagagtt tcatccgttt ggttaagaaa acattccttc aattcatcta 240
tggcatttgt agtggcattg tcgtctatga actcttgaag aagttctttg tattcagtct 300
tagacacttg tggattgatt gncttggaaa tcacattctc caataaggga cctcgg 360
<210> 218
<211> 321
<212> DNA
<213> Homo sapiens
<400> 218
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ctgctctgcc aatttctgga tttctttatt ttcagcaaac actttcttta aagcttgact 120
gtgtgggcac tcatccaagt gatgaataat catcaagggt ttgttgcttg tcttggattt 180
atatagaget tetteatatg tetgagteea gatgagttgg teaccecaae etetggagag 240
ggtctggggc agtttgggtc gagagtcctt tgtgtccttt ttggctccag gtttgactgt 300
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ggtatctctg gacctgcctg g
                                                                   321
<210> 219
<211> 271
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (41)
<223> n=A,T,C or G
<400> 219
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accetatgge ttacaaagta gagttggeec agttteette cacetgaggg gageactetg 120
actectaaca gtetteettg coetgecate atetggggtg getggetgte aagaaaggee 180
gggcatgctt tctaaacaca gccacaggag gcttgtaggg catcttccag gtggggaaac 240
agtcttagat aagtaaggtg acttgtctaa g
<210> 220
<211> 351
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(351)
<223> n=A,T,C or G
<400> 220
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cctgcccgaa tttgctgact gggctcagga acagggagat gctcctgcca ttttatttga 120
caaagagttc tgcgagtgga tgatccagca aatagggcca aaacttgatg ggaaaatccc 180
ggtgtccaga gggtttccta tcgctgaagt gttcacgctg aagcccctgg agtttggcaa 240
gcccaacact ttggtctgtt ttgtcagtaa tctcttccca cccatgctga cagtgaactg 300
gtagcatcat tccgtccctg tggaaggatt tgggcctact tttgtctcag a 360
<210> 221
<211> 371
<212> DNA
<213> Homo sapiens
<400> 221
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accgtgctgg ggacggcacc gcgtcaggat gcaggcagat ccctgcagaa gtgtctaaaa 120
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acgaacggtg tcgtcgaaac agcagccctt atttgcacac tgggagggcg tgacaccagg 240
aaaaccacaa ttctgtcttt cacggggggc cactgtacac gtctctgtct gggcctcggc 300
cagggtgccg agggccagca tggacaccag gaccagggcg cagatcacct tgttctccat 360
ggtggacctc g
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<210> 222
<211> 471
<212> DNA
<213> Homo sapiens
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<400> 222
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agggaaataa ggttagagaa aggatccggg caatcttaag gactgaggaa gacatgttcc 120
ccaaccettg aacteacaaa ccctgaaget caaggattge atcetteete caaateteac 180
tcaacataat aagtgcagaa caacatgcca aagcactgta tgaagcacta gggacaaaga 240
caaggtcaaa atccttgtaa ccaaatttaa tggtattgta atgcagtgtt aacacaggac 300
agtaacagaa cacccaagaa ccaaacagaa gagggtaggg ataagcataa atgaagtaac 360
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<222> (31)
<223> n=A,T,C or G
<400> 224
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cttaatctga ttgtccaaat cattaaaata tggatgattc agtgccattt tgccagaaat 180
tcgtttggct ggatcataga ttaacatttt cgagagcaaa tccaagccat tttcatccaa 240
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<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (34)
<223> n=A,T,C or G
<400> 225
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ccagtaggca ggaagatggc tttgggcagt ggctggatga aagcagattt gagataccca 180
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gatcattctc t
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<211> 331
<212> DNA
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<221> unsure
<222> (1)...(331)
<223> n=A,T,C or G
<400> 226
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tgtagggtgc agtctttact ccctaacccg tttcccgaaa aaggtgctac ctcctttcca 180
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cctggagcac gggaggggag gtgacggctg gtgactgatg gatgggtagt gggctgagaa 300
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<211> 391
<212> DNA
<213> Homo sapiens
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<211> 391
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<213> Homo sapiens
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<222> (35)
<223> n=A,T,C or G
<400> 228
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gcttgtctga atagatttga gcaacagtct tgcttttgtt aaaatcctgg agccgttaag 300
tcctgaatat tcttctggac atcattgctg gctggagaaa ggagccccag gcccggctcg 360
gctgacatct gtcaggtttg gaagtctcat c
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<211> 341
<212> DNA
<213> Homo sapiens
<220>
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<222> (202)
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<211> 511
<212> DNA
<213> Homo sapiens
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Cttcagttgt ctgaagaatg gttttatgcc cacatcatac cattccttgg atgaaacccq 180
tatagttcac aatagagete agggageeee taactettee aaaccacatg ggagaeagtt 240
teetteatge ccaageetga geteagatee agettgeaac taateettet ateatetaac 300
atgccctact tggaaagatc taagatctga atcttatcct ttgccatctt ctgttaccat 360
atggtgttga atgcaagttt aattaccatg gagattgttt tacaaacttt tgatgtggtc 420
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<211> 311
<212> DNA
<213> Homo sapiens
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gctccctgga gccctgttgg cagctctagc tttgcagtcg tgtaattggc ccaaqtcatt 240
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ggggtggacc t
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<210> 232
<211> 351
<212> DNA
<213> Homo sapiens
<400> 232
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aaatttttat atgtgttatt gattgtcgtg taacaaatgg cccccacaaa ttagtagctt 240
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<211> 221
<212> DNA
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<210> 235
<211> 381
<212> DNA
<213> Homo sapiens
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<221> misc_feature
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<223> n=A,T,C or G
<400> 235
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gacctataac ctctccagaa agaccactct gtgtggcatc acagtccaca cagtttaagg 180
aaatatttag acttaacaat cagacaccag ctcttactca cacttacact cacagcccac 240
acacaagtgt gcaaacatac acacacatat atattteetg atacatteat ggaatateag 300
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<210> 236
<211> 441
<212> DNA
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<213> Homo sapiens
<400> 236
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tgctctgttg tgtcacatga g
<210> 237
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(281)
<223> n=A,T,C or G
<400> 237
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ttccctcttt acatttttct tgtttctttc cttatttatc tttgtccatc ttgagatcta 180
ctgtaaagtg aatnttttaa tgaaaacann nccaagttnt actctcactg ggnrtgggac 240
atcagatgta attgagaggc caacaggtaa gtcttcatgt c
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<210> 238
<211> 141
<212> DNA
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<223> n=A,T,C or G
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attaaataaa catcgctaaa g
<210> 239
<211> 501
<212> DNA
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<220>
<221> misc_feature
<222> (1) ... (501)
<223> n=A,T,C or G
<400> 239
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cctaaactat actaaagccc ttttcccatg catggatgga aatggaagat tttttttaa 180
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<213> Homo sapiens
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<210> 241
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<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(411)
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<400> 241
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ggtatcaggg ttagagcttc agcctccagt gtgatggtat cagggttaga gcttcagcct 180
ccagtgtgat ggtatcgggg ttagatcttc aatccccagt ggtggtggtt agagcttcaa 240
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tgggggtttt aagatgtaat tagggtttaa gatcataagg gacctggtct gatggggatt 360
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<210> 242
<211> 351
<212> DNA
<213> Homo sapiens
<400> 242
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tggtcctgcc cctttgaggg ggtgcaaaca tgactgggac ctaagagcca gaggctgtgt 240
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<400> 243
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acacgtaaag gatggaacct aatcetetee egagaegeet cetttgtgtt aatgeetatt 180
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<211> 301
<212> DNA
<213> Homo sapiens
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<210> 245
<211> 391
<212> DNA
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<210> 246
<211> 291
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(291)
<223> n=A,T,C or G
<400> 246
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gagctggcaa ggtgcaaagn cntctgcaga atattcacca ggttgacaca gacctccaca 120
ttcagacata ttccaagctt ctggggtctt cagggcccca gaatttcctg gtcttgggca 180
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<210> 247
<211> 471
<212> DNA
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<221> misc_feature
<222> (1)...(471)
<223> n=A,T,C or G
<400> 247
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acaacaggag tacatacagn gaaccaaaaa gagtgtacca ggaggagcan accctgaaca 120
gttanaacta tggaaatcgc tatgctttgt gttgtcacag gagttaaaat aggaataccc 180
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<210> 248
<211> 551
<212> DNA
<213> Homo sapiens
<400> 248
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<210> 249
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<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(181)
<223> n=A,T,C or G
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cacaatgtct tcacctccac aggggctcat cacggnggtc agggcaaggg cccccagcat 120
cagagetttg tttaggatca teetetteee aaggeageet tageagttge tgaeetgeee 180
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77.

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<210> 251
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tataattaaa ctgtctgttt aggagaagct gaatccagaa gaaacacaag ctgtaaagtg 240
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<213> Homo sapiens
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gaatgtaaga ccaagacaca aaaatcaatt acatttctat ataatagcaa tgaacagata 180
ctgaaatttt aaaaactaaa tcattttaca aaagtatcac aatatgaaac actccgggat 240
aaattggata aaagatgtgc aagactgtac aaaagctaca aaacatttat gaaggaaatt 300
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aaacaagcta agacaagtat tggagaagta tagaagatag aaaaat
<210> 253
<211> 544
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (224)
```

```
<223> n=A,T,C or G
<400> 253
gaaggagttc agtagcaaag tcacacctgt ccaattccct gagctttgct cactcaqcta 60
atgggatggc aaaggtggtg gtgctttcat cttcaggcag aagcctctgc ccatccccct 120
caagggctgc aggcccagtt ctcatgctgc ccttgggtgg gcatctgtta acagaggaga 180
acgtctgggt ggcggcagca gctttgctct gagtgcctac aaanctaatg cttggtgcta 240
gaaacatcat cattattaaa cttcagaaaa gcagcagcca tgttcagtca ggctcatgct 300
geoteactge traagtgeet geaggageeg cetgeeaage teceetteet acacetggea 360
cactggggtc tgcacaaggc tttgtcaacc aaagacagct tccccctttt gattgcctgt 420
agactttgga gccaagaaac actctgtgtg actctacaca cacttcaggt ggtttgtgct 480
tcaaagtcat tgatgcaact tgaaaggaaa cagtttaatg gtggaaatga actaccattt 540
ataa
<210> 254
<211> 339
<212> DNA
<213> Homo sapiens
<400> 254
tggcattcag ggcagtgtct tctgcatctc ctaggaacct cgggagcggc aqctccqqcq 60
cctggtagcg agaggcgggt tccggagatc ccggcctcac ttcgtcccac tgtggttagq 120
ggtgagtcct gcaaatgtta agtgatttgc tcaaggtgcc catttcgcag gaattggagc 180
ccaggccagt tctctgagcc tatcattagg gctaaaggag tgcgtgatca gaatggtgtc 240
tggacggttc tacttgtcct gcctgctgct ggggtccctg ggctctatgt gcatcctctt 300
cactatctac tggatgcagt actggcgtgg tggctttgc
                                                                   339
<210> 255
<211> 405
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(405)
<223> n=A,T,C or G
<400> 255
gaggtttttt ntttttttt ttttttttt caattaaana tttgatttat tcaaqtatqt 60
gaaaacattn tacaatggaa acttttntta aatgctgcat gtnctgtgct atggaccacn 120
cacatacagc catgctgttt caaaaaactt gaaatgccat tgatagttta aaaactntac 180
ncccgatgga aaatcgagga aaacaattta atgtttcatn tgaatccana ggngcatcaa 240
attaaatgac agctccactt ggcaaataat agctgttact tgatggtatc caaaaaaaaa 300
tggttgggga tggataaatt caaaaatgct tccccaaagg ngggnggttt ttaaaaaagtt 360
tcaggncaca accettgcan aaaacactga tgcccaacac antga
<210> 256
<211> 209
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (6)
<223> n=A,T,C or G
```

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<400> 256
gggcangtct ggtcctctcc ccacatgtca cactctcctc agcctctccc ccaacctgc 60
tetecetect eccetgeett ageceaggga eagagtetag gaggageetg gggeagaget 120
ggaggcagga agagagcact ggacagacag ctatggtttg gattggggaa gaggttagga 180
agtaggttct taaagaccct tttttagta
<210> 257
<211> 343
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(343)
<223> n=A,T,C or G
<400> 257
tetggacace ataateeett ttaagtgget ggatggteac aceteteeea ttgacaaget 60
gggttaagtc aataggttga ctaggatcaa cacgacccaa atcaataaga tactgcagtc 120
tattgagact caaaggetta tactggegte tgaaactatg teettegtta aaccegtatt 180
ttgggattcg gatgtaaaat ggagtctggc ctccctcaaa gcccaagcgg ggccgggttc 240
ctetttgeet tteteettta tggeetetge eacattttet acetettete egacetettg 300
gtcttntctc nggtttcttg gagccgggat tcggctttaa gtn
<210> 258
<211> 519-
<212> DNA
<213> Homo sapiens
<400> 258
gcggcttctg acttctagaa gactaaggct ggtctgtgtt tgcttgtttg cccacctttg 60
gctgataccc agagaacctg ggcacttgct gcctgatgcc cacccctgcc agtcattcct 120
ccattcaccc agcgggaggt gggatgtgag acagcccaca ttggaaaatc cagaaaaccg 180
ggaacaggga tttgcccttc acaattctac tccccagatc ctctcccctg gacacaggag 240
acceacaggg caggaceeta agatetgggg aaaggaggte etgagaacet tgaggtacee 300
ttagateett ttetaceeac ttteetatgg aggatteeaa gteaceaett eteteacegg 360
cttctaccag ggtccaggac taaggcgttt tctccatagc ctcaacattt tgggaatctt 420
cccttaatca cccttgctcc tcctgggtgc ctggaagatg gactggcaga gacctctttg 480
ttgcgttttg tgctttgatg ccaggaatgc cgcctagtt
                                                                  519
<210> 259
<211> 371
<212> DNA
<213> Homo sapiens
<400> 259
attgtcaact atatacacag tagtgaggaa taaaatgcac acaaaacaat ggatagaata 60
tgaaaatgtc ttctaaatat gaccagtcta gcatagaacc ttcttctctt ccttctcagg 120
tottocaget ceatgicate taacceacti aacaaacgig gacgiatege ticcagagge 180
cgtcttaaca actccatttc caaaagtcat ctccagaaga catgtatttt ctatgatttc 240
ttttaaacaa atgagaattt acaagatgtg taactttcta actctatttt atcatacgtc 300
ggcaacctct ttccatctag aagggctaga tgtgacaaat gttttctatt aaaaggttgg 360
ggtggagttg a
```

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<210> 260
 <211> 430
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(430)
 <223> n=A,T,C or G
<400> 260
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tactatattt attgtcaaag agtggtacat aggtgagtgt tcatcttccc tctcatgccg 120
gtatactctg cttcgctgtt tcagtaaaag ttttccgtag ttctgaacgt cccttgacca 180
caccataana caagcgcaag tcactcanaa ttgccactgg aaaactggct caactatcat 240
ttgaggaaag actganaaag cctatcccaa agtaatggac atgcaccaac atcgcggtac 300
ctacatgttc ccgtttttct gccaatctac ctgtgtttcc aagataaatt accacccagg 360
gagtcacttc ctgctatgtg aacaaaaacc cggtttcttt ctggaggtgc ttgactactc 420
tctcgngagc
                                                                   430
<210> 261
<211> 365
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (178)
<223> n=A,T,C or G
<400> 261
tectgaegat agecatgget graceaetta actatgatte tattecaaet gtteagaate 60
atatcacaaa atgacttgta cacagtagtt tacaacgact cccaagagag gaaaaaaaaa 120
aaaaaagacg cctcaaaatt cactcaactt ttgagacagc aatggcaata ggcagcanag 180
aagctatgct gcaactgagg gcacatatca ttgaagatgt cacaggagtt taagagacag 240
gctggaaaaa atctcatact aagcaaacag tagtatctca taccaagcaa aaccaagtag 300
tatctgctca gcctgccgct aacagatctc acaatcacca actgtgcttt aggactgtca 360
ccaaa
                                                                   365
<210> 262
<211> 500
<212> DNA
<213> Homo sapiens
<400> 262
cctagatgtc attigggacc cttcacaacc attitgaagc cctgtttgag tccctgggat 60
atgtgagetg titetatgea taatggatat teggggttaa caacagteee etgettgget 120
tctattctga atccttttct ttcaccatgg ggtgcctgaa gggtggctga tgcatatggt 180
acaatggcac ccagtgtaaa gcagctacaa ttaggagtgg atgtgttctg tagcatccta 240
tttaaataag cctattttat cctttggccc gtcaactctg ttatctgctg cttgtactgg 300
tgcctgtact tttctgactc tcattgacca tattccacga ccatggttgt catccattac 360
ttgatcctac tttacatgtc tagtctgtgt ggttggttggt gaataggctt ctttttacat 420
ggtgctgcca gcccagctaa ttaatggtgc acgtggactt ttagcaagcg ggctcactgg 480
aagagactga acctggcatg
```

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<210> 263
 <211> 413
 <212> DNA
 <213> Homo sapiens
<400> 263
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caggatgtct gacttcaaat tgaaactccc aaagtaatga gtttggaagg gtggggtgtq 120
gcctttccag gatgggggtc ttttctgctc ccagcggata gtgaaacccc tgtctgcacc 180
tggttgggcg tgttgctttc ccaaaggttt tttttttagg tccgtcgctg tcttgtggat 240
taggcattat tatctttact ttgtctccaa ataacctgga gaatggagag agtagtgacc 300
ageteaggge cacagtgega tgaggaceat etteteacet etetaaatge aggaagaaac 360
gcagagtaac gtggaagtgg tccacaccta ccgccagcac attgtgaatg aca 420
<210> 264
<211> 524
<212> DNA
<213> Homo sapiens
<400> 264
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cattccaccc cactcatcgt ctgtgcacct atgttcaaac tttctccaca gttccccaat 120
gaagaagact catttcataa gtttgtggct cctgaagaag tcctgccatt cacagaaggg 180
gacattetgg agaaggteag egtgeattge cetgtgtttg actaegttee eccagagete 240
attaccetet ttatetecaa cattggtggg aatgeacett cetacateta cegeetgatg 300
agtgaactct accatcctga tgatcatgtt ttatgaccga ccacacgtgt cctaagcaga 360
ttgcttaggc agatacagaa tgaagaggag acttgagtgt tgctgctgaa gcacatcctt 420
ctttttagtc accccgtaac aagggcacac atccaggact gtgt
<210> 265
<211> 344
<212> DNA
<213> Homo sapiens
<400> 265
teetteette taetteagga gatgatteaa agttaettgt ggacatttet ttaagttetg 60
aagacaaatg agacaggatt tggcctgcgg gttcttcaga cttctctacc acctccatta 120
actiticate tiggetigae graggeaatg cactatitig etetitigtt tetiggagatg 180
acccagcacc acttctttct cttggcgggg ttctaagtgt gtctttgaat accagtgaag 240
actraggert attetgtact ggaaagggac taaatttgte tttetgteta ggaggtgatg 300
cagtagcatc ctcctgaggg ggtaaggcca ttttctcttt ttga
                                                                344
<210> 266
<211> 210
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature .
<222> (78)
<223> n=A,T,C or G
<400> 266
ccacaatgtc cataacttga gcaggctttg gcatcccacc accccttca gaccaataca 60
```

```
cactatgttg gaggaacnac tttaaaatgt aaaatgagaa atgggcactg aacactccat 120
cctcactccc aacagcccac ccacacact cttcaactgc tatccaaaca tggaggagct 180
cttgtggaag agaggctcaa caccaaataa
                                                                   210
<210> 267
<211> 238
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(238)
<400> 267
tcggncctcc caccctctna ctgaaattct ntgaaattct cccctttggg atgaggatgg 60
caaccccagg catgtaccct cccaacctgg gacccgacct aataccctaa catcctgctg 120
acagtggctg ttctcgctgg gcaggcgtcc caaagcacat cgagccagat tcaggcagag 180
tggaactggc ccctcagcca tcagtggagg tggcctggga ggctctaccc tgaacggg 240
<210> 268
<211> 461
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (459)
<223> n=A,T,C or G
<400> 268
tecteaagga catgeeeett gatagaaact cagtteetgt etceagttee etcetggaee 60
tgatccccca aatgcagggc ctgggactat atccagttcc ttattttcag aggcccatgc 120
acaagatgca cagcaaataa gtgctgaata aagacccagc tactgctagc ttaccctgct 180
ccaaacattc accaagtcct cagcaaagag ggccatccat tcacctcttc taaaaacaca 240
ctgagetece cagtetatae eccaagatat gettggetee caactatece teeteteta 300
tctccaagcc agtttcccct ttctaagtat actgatatta ccaaagacac tgacaatctt 360
cttttcctac ctctccccag tgactaggtt tgcagcagga gctctataag tcctagtata 420
cagcagaagc tccataaatg tgtgctgacc taacattang c
<210> 269
<211> 434
<212> DNA
<213> Homo sapiens
ctgtgttggt gagcaccgat tcccactcaa tatggcgtgg cttacagtct tcattaggtt 60
cccgctccca accagaatga ggaatgatca cttcatctgt caaggcatgc agtgcatggt 120
ccacaatctc cattttgatt gagtcatggg atgaaagatt ccacagggtt ccggtaataa 180
Cttcagtaag gtccatatca cgagcctttc gaagcaatcg cacaagggca ggcacaccat 240
cacagttttt tatggcaatc ttgttatcct ggtcacgtcc aaaagagata ttcttgagag 300
ctccacaggc tccaaggtgc acttcctttt tgggatggtc taacaatccc accagtactg 360
ggatgccctt gagcttccgc acgtcagtct tcaccttgtc attgcggtag cataagtgtt 420
gcaggtatgc aaga
```

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<211> 156
<212> DNA
<213> Homo sapiens
<400> 270
ctgcaccagc gattaccagt ggcattcaaa tactgtgtga ctaaggattt tgtatgctcc 60
ccagtagaac cagaatcaga caggtatgag ctagtcaaca gcaagtcttt gttggattcq 120
agtaggctca ggatctgctg aaggtcggag gagtta
<210> 271
<211> 533
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(533)
\langle 223 \rangle n=A,T,C or G
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tgaagaactt agaagctgtg gagaccttgg ggtccacgtn caccatctgc tctgataaaa 120
ctggaactct gactcanaac cggatgacag tggcccacat gtggtttgac aatcaaatcc 180
atgaagctga tacgacagag aatcagagtg gtgtctcttt tgacaagact tcagctacct 240
ggcttgctct gtccagaatt gcaggtcttt gtaacagggc agtgtttcag gctaaccagg 300
aaaacctacc tattcttaag cgggcagttg caggagatgc ctctgagtca gcactcttaa 360
agtgcataga gctgtgctgt ggntncgtga aggagatgag agaaagatac nccaaaatcg 420
tegagatace etteaactee accaacaagt accagttgte tatteataag aaccecaaca 480
catcggagcc ccaacacctg ttggtgatga agggcgccc agaaaggatc cta 540
<210> 272
<211> 630
<212> DNA
<213> Homo sapiens.
<400> 272
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ttttcttcgc cttcccgtac ttctgtcttc cagttttcca cttcaaactt ctatcttctc 120
caaattgttt catcctacca ctcccaatta atctttccat tttcgtctgc gtttagtaaa 180
tgcgttaact aggetttaaa tgacgcaatt etecetgegt catggattte aaggtetttt 240
aatcaccttc ggtttaatct ctttttaaaa gatcgccttc aaattatttt aatcacctac 300
aacttttaaa ctaaacttta agctgtttaa gtcaccttca ttttaatcta aaagcattqc 360
cettetattg gtattaatte ggggetetgt agteettet etcaatttte tittaaatae 420
attititact ccatgaagaa getteatete aaceteegte atgittitaga aacettitat 480
Cttttccttc ctcatgctac tcttctaagt cttcatattt tctcttaaaa tcttaagcta 540
ttaaaattac gttaaaaact taacgctaag caatatctta gtaacctatt gactatattt 600
tttaagtagt tgtattaatc tctatctttc
                                                                   630
<210> 273
<211> 400
<212> DNA
<213> Homo sapiens
<400> 273
tetggtttge cetecagtte attetgaate tagaettget cageetaate aagtteetgt 60
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acaaccagaa gcgacacagg ttcctttggt atcatccaca agtgaggggt acacagcatc 120
 tcaaccettg taccageett etcatgetae agageaacga ccacagaagg aaccaattga 180
 tcagattcag gcaacaatct ctttaaatac agaccagact acagcatcat catcccttcc 240
 tgctgcgtct cagcctcaag tatttcaggc tgggacaagc aaacctttac atagcagtgg 300
 aatcaatgta aatgcagete cattecaate catgcaaacg gtgttcaata tgaatgeece 360
 agttcctcct gttaatgaac cagaaacttt aaaacagcaa
 <210> 274
 <211> 351
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (2)
<223> n=A,T,C or G
<400> 274
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gaccttgatg cttggagcat tctcattcga gaggcacaga atcaacctat agacaaaqca 120
cggaagactt atgaacgcct tgttgcccag ttccccagtt ctggcagatt ctggaaactg 180
tacattgaag cagaggttac tattttattt tattttttct tatatcagta ttgcagcatt 240
cactgtagtg atagaaaaca agttaggaac atagccaatt aggacaagga ggatttaaat 300
gtgtcttacc tttattttgt aaaataggta taaaggagta attaaaatga a 360
<210> 275
<211> 381
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(381)
<223> n=A,T,C or G
<400> 275
gcgnggtcgc nnncgaggtc tgagaagccc ataccactat ttgttgagaa atgtgtggaa 60
tttattgaag atacagggtt atgtaccgaa ggactctacc gtgtcagcgg gaataaaact 120
gaccaagaca atattcaaaa gcagtttgat caagatcata atatcaatct agtgtcaatg 180
gaagtaacag taaatgctgt agctggagcc cttaaagctt tctttgcaga tctgccagat 240
cctttaattc catattctct tcatccagaa ctattggaag cagcaaaaat cccggataaa 300
acagaacgtc ttcatgcctt gaaagaaatt gttaagaaat ttcatcctgt aaactatgat 360
gtattcagat acgtgataac a
<210> 276
<211> 390
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (5)
<223> n=A,T,C or G
<400> 276
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```
gctcngactc cggcgggacc tgctcggagg aatggcgccg ccgggttcaa gcactgtctt 60
 cctgttggcc ctgacaatca tagccagcac ctgggctctg acgcccactc actacctcac 120
 caagcatgac gtggagagac taaaagcctc gctggatcgc cctttcacaa atttggaatc 180
 tgccttctac tccatcgtgg gactcagcag ccttggtgct caggtgccag atgcaaagaa 240
 agcatgtacc tacatcagat ctaaccttga tcccagcaat gtggattccc tcttctacgc 300
 tgcccaggcc agccaggccc tctcaggatg tgagatctct atttcaaatg agaccaaaga 360
 tctgcttctg gcagacctcg gccgcgacca
 <210> 277
 <211> 378
 <212> DNA
 <213> Homo sapiens
 <400> 277
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 cgatggtttt ggaccattta tgccgggatt cgacatcatt ccctataatg atctgcccqc 120
 actggagcgt gctcttcagg atccaaatgt ggctgcgttc atggtagaac caattcaggg 180
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 caggcaccag gttctcttta ttgctgatga aatacagaca ggattggcca gaactggtag 300
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 ttctgggggc ttataccc
                                                                   378
 <210> 278
 <211> 366
 <212> DNA
 <213> Homo sapiens
<400> 278
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agcttgtgaa actgttgcta aaactggaat gatccttctt gctggggaaa ttacatccag 180
agctgctgtt gactaccaga aagtggttcg tgaagctgtt aaacacattg gatatgatga 240
ttcttccaaa ggttttgact acaagacttg taacgtgctg gtagccttgg agcaacagtc 300
accagatatt gctcaaggtg ttcatcttga cagaaatgaa gaagacattg gtgctggaga 360
ccaggg
<210> 279
<211> 435
<212> DNA
<213> Homo sapiens
<400> 279
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tggaagacct acaacccaag gatggaaggc ccctgtcaca aagcctacct agatggatag 120
aggacccaag cgaaaaagat atctcaagac taacggccgg aatctggagg cccatgaccc 180
agaacccagg aaggatagaa gcttgaagac ctggggaaat cccaagatga gaaccctaaa 240
coctacetet titetatigt tracactiet tactetraga tatticeagt tetecrigitt 300
atctttaagc ctgattettt tgagatgtac tttttgatgt tgeeggttac etttagattg 360
acaagtatta tgcctggcca gtcttgagcc agctttaaat cacagctttt acctatttgt 420
taggctatag tgttt
<210> 280
<211> 435
<212> DNA
<213> Homo sapiens
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<400> 280
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caatgatgag aacctgcgca tagtggtggg taacctgttc cttgccggga tggtgaccac 180
ctcgaccacg ctggcctggg gcctcctgct catgatccta cacctggatg tgcagcgtga 240
geccagacet gteegggegg cegetegaaa tteeageaca etggeggeeg ttactagtgg 300
atccgagete ggtaccaage ttggegtaat catggteata getgttteet gtgtgaaatt 360
gttatccgct cacaattcca cacaacatac gagccggaag cataaagtgt aaagcctggg 420
gtgcctaatg agtga
<210> 281
<211> 440
<212> DNA
<213> Homo sapiens
<400> 281
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gctgctgaga tgggaaaggg ctccttcaag tatgcctggg tcttggataa actgaaagct 120
gagcgtgaac gtggtatcac cattgatatc tccttgtgga aatttgagac cagcaagtac 180
tatgtgacta tcattgatgc cccaggacac agagacttta tcaaaaacat gattacaggg 240
acateteagg etgaetgtge tgteetgatt gttgetgetg gtgttggtga atttgaaget 300
ggtateteca agaatgggea gaceegagag catgeeette tggettacae aetgggtgtg 360
aaacaactaa ttgtcggtgt taacaaaatg gattccactg agccccctac agccagaaga 420
gatatgagga aattgttaag
<210> 282
<211> 502
<212> DNA
<213> Homo sapiens
<400> 282
tctgtggcgc aggagccccc tcccccggca gctctgacgt ctccaccgca gggactggtg 60
cttctcggag ctcccactcc tcagactccg gtggaagtga cgtggacctg gatcccactg 120
atggcaaget etteeceage gatggtttte gtgaetgeaa gaagggggat cecaageaeg 180
ggaagcggaa acgaggccgg ccccgaaagc tgagcaaaga gtactgggac tgtctcgagg 240
gcaagaagag caagcacgcg cccagaggca cccacctgtg ggagttcatc cgggacatcc 300
tcatccaccc ggagctcaac gagggcctca tgaagtggga gaatcggcat gaaggcgtct 360
tcaagttcct gcgctccgag gctgtggccc aactatgggg ccaaaagaaa aagaacagca 420
acatgaccta cgagaagctg agccgggcca tgaggtacta ctacaaacgg gagatcctqq 480
aacgggtgga tggccggcga ct
<210> 283
<211> 433
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(433)
<223> n=A,T,C or G
<400> 283
ccatattaga ttactggaac atctaagcat cagtgtgtga ccatgcgaac aaaagacttc 60
9999agtgtc tatttttaaa aaggtttatg tgtgtcgagg cagttgtaaa agatttactg 120
```

```
cagaatcaan cccactttta ggcttangac caggttctaa ctatctaaaa atattgactg 180
ataacaaaaa gtgttctaaa tgtggctatt ctgatccata nttgnttttt aaagaaaaaa 240
antgtntata cagaaagagt ntaaaagttc tgtgaattna atgcaaatta gncnccantc 300
ttgacttccc aaanacttga ttnatacctt tnactcctnt cnnttcctgn ncttcnttaa 360
nntcaatnat tnggnagtnn anggconton gnanaacaco nttncncgnt concgcaato 420
cancegeett nan
                                                                   433
<210> 284
<211> 479
<212> DNA
<213> Homo sapiens
<400> 284
tctggaagga tcagggatct gagcaaagcc aagtttactt aagctaagcc acttgttcct 60
gggtcaagca gtttgttttc taataagcat cattcctgat cattagagca aagggatgaa 120
tgctcctctt ggaatgatac aggggatctg ccactgggag agtgttgctc agtgttagag 180
tagcagcaat gacagaatga cagcgactct ctgagtcaac ccagtacttt tagtaccccg 240
teactatgtg aataaaggea getagaaaat ggaeteaatt etgeaageet teatggeaac 300
agcccatatt aagacttcta gaacaagtta aaaaaaaatc ttccatttcc atccatgcat 360
gggaaaaggg ctttagtata gtttaggatg gatgtgtgta taataataaa atgataagat 420
atgcatagtg ggggaataaa gcctcagagt ccttccagta tggggaatcc attgtatct 480
<210> 285
·<211> 435
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(435)
<223> n=A,T,C or G
<400> 285
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tcatccttat gtaacaaaat gtnttcttan aanaanaaat atattatttc aggtcataaa 120
taatcagcaa acatacaact gttggcaact aaaaaaaaac ccaacactgg tattttccat 180
cagngctgaa aacaaacctg cttaaanata tatttacagg gatagtncag tnctcaaaaa 240
caaaaattga ggtattttgg ttcttctagg agtagacaat gacattttgg gangggcaga 300
cccctnnccc aaaaaataaa ataagggnat nttcttcant atngaanann gggggcgccc 360
cggggaaaan naaaccttgg gnngggggtt tggcccaagc ccttgaaaaa aaantttntt 420
tcccaaaaaa aacng
                                                                  435
<210> 286
<211> 301
<212> DNA
<213> Homo sapiens
<400> 286
cctggtttct ggtggcctct atgaatccca tgtagggtgc agaccgtact ccatccctcc 60
ctgtgagcac cacgtcaacg gctcccggcc cccatgcacg ggggagggag atacccccaa 120
gtgtagcaag atctgtgagc ctggctacag cccgacctac aaacaggaca agcactacgg 180
atacaattcc tacagcgtct ccaatagcga gaaggacatc atggccgaga tctacaaaaa 240
cggccccgtg gagggagett tetetgtgta tteggaette etgetetaca agteaggagt 300
```

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<210> 287
<211> 432
<212> DNA
<213> Homo sapiens
<400> 287
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acggcaccag ctttgcagac ggcaagggac acccccagaa tggcgttcgc accaaactta 180
gatttatttt ctgttccatc catctcgatc atcagtttgt caatcttctc ttgttctgtg 240
acgttcagtt tcttgctaac cagggcaggc gcaatagttt tattgatgtg ctcaacagcc 300
tttgagacac cetteeceat atagegagte ttateattgt eeeggagete tagggeetea 360
tagataccag tigaagcacc acigggcaca gcagciciga agagacciit igaggigaag 420
agatcaacct ca
<210> 288
<211> 326
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (254)
<223> n=A,T,C or G
<400> 288
totggotcaa gtcaaagtoo tggtootott otocgootoo ttottoatoa tagtaataaa 60
cgttgtcccg ggtgtcatcc tctgggggca gtaagggctc tttgaccacc gctctcctcc 120
gaagaaacag caagagcagc agaatcagaa ttagcaaagc aagaattcct ccaagaatcc 180
ccagaatggc aggaatttgc aatcctgctt cgacaggctg tgccttccta cagacgccgg 240
eggecectte acanteacae aegetgaeet etaaggtggt eaettggtet ttattetggt 300
tatccatgag cttgagattg attttg
<210> 289
<211> 451
<212> DNA
<213> Homo sapiens
<400> 289
gtcccggtgt ggctgtgccg ttggtcctgt gcggtcactt agccaagatg cctgaggaaa 60
cccagaccca agaccaaccg atggaggagg aggaggttga gacgttcgcc tttcaggcag 120
aaattgccca gttgatgtca ttgatcatca atactttcta ctcgaacaaa gagatctttc 180
tgagagaget cattteaaat teateagatg cattggaeaa aateeggtat gaaagettga 240
cagatcccag taaattagac tctgggaaag agctgcatat taaccttata ccgaacaaac 300
aagatcgaac teteactatt gtggataetg gaattggaat gaccaagget gacttgatea 360
ataaccttgg tactatcgcc aagtctggga ccaaagcgtt catggaagct ttgcaggctg 420
gtgcagatat ctctatgatt ggacctcggc c
                                                                   451
<210> 290
<211> 494
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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```
<222> (421)
<223> n=A,T,C or G
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tcaattgtga catctagatg gcttaagatt actttctggt ggtcacccat gctgaacaat 120
atttttcaat cttccaaaca gcaaagactc aaaagagatt ctgcatttca catcagttca 180
caagttcaag agtcttccat ttatcttagc ttttggaata aattatcttt gaggtagaag 240
gacaatgacg aagccactta attccttgtg tctgcataaa agcagattta ttcatcacaa 300
cttcatttat gtgaataaag cagatgatga taaaatgttc tcttattctt gtttaatcag 360
tagtggtagt gatgccagaa acttgtaaat gcacttcaaa ccaattgtgg ctcaagtgta 420
ngtggttccc caaggctggt accaatgaga ctggggtttg ggaattagtt ggtcatcatc 480
cctcctgctg ccca
<210> 291
<211> 535
<212> DNA
<213> Homo sapiens
<400> 291
tcgcgtgctt aacatgaaaa caaactttgt gctgtttggt tcattgtatg cattgatgga 60
gtcttgtctc tcatcatggg gtgtctgacc atccaacctg cagtactcat aatttctcca 120
catgcaataa tcttccaaaa tgtccaatac ccttgtcatt tgactgaaga ttagtactcg 180
tgaaccttgt tcttttaact tagggagcag cttgtctaaa accaccattt tgccactgtt 240
ggttactaga tgcatatctg ttgtataagg tggaccaggt tctgctccat caaagagata 300
tggatgatta caacattttc tcaactgcat taggatgttc aataacctca ttttqtccat 360
cttgcctgct gagttgagta tatctatatc cttcattaat accgagtat accattccct 420
ttgcattttg ctgaggccca catagatttt tacttccttc tttggaggca aactcttttc 480
aacatcagcc ttaattcgac gaaggaggaa tggacgcaaa accatatgaa gcctc 540
<210> 292
<211> 376
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(376)
<223> n=A,T,C or G
<400> 292
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aaaattggag cctgcccctc ggcccataag cccttgttgg gaactgagaa gtgtatatgg 120
ggcccaagct actggtgcca gaacacagag acagcagccc agtgcaatgc tgtcgagcat 180
tgcaaacgcc atgtgtggaa ctaggaggag gaatattcca tcttggcaga aaccacagca 240
ttggtttttt tctacttgtg tgtctggggg aatgaacgca cagatctgtt tgactttgtt 300
ataaaaatag ggctccccca cctcccccat ttttgtgtcc tttattgnag cattgctgtc 360
tgcaagggag ccccta
<210> 293
<211> 320
<212> DNA
<213> Homo sapiens
<400> 293
```

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90

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cctcgcatgg cctgcagtct ggcagcagcc ccgagttgtt tcctcgctga tcgatttctt 120
tectecaggt agagttttet ttgettatgt tgaatteeat tgeetettt eteateacag 180
aagtgatgtt ggaatcgttt cttttgtttg tctgatttat ggttttttta agtataaaca 240
aaagtttttt attagcattc tgaaagaagg aaagtaaaat gtacaagttt aataaaaagg 300
ggccttcccc tttagaatag
<210> 294
<211> 359
<212> DNA
<213> Homo sapiens
<400> 294
ctgtcataaa ctggtctgga gtttctgacg actccttgtt caccaaatgc accatttcct 60
gagacttgct ggcctctccg ttgagtccac ttggctttct gtcctccaca gctccattgc 120
cactgttgat cactagettt ttettetgee cacacettet tegactgttg actgeaatge 180
aaactgcaag aatcaaagcc aaggccaaga gggatgccaa gatgatcagc cattctggaa 240
tttggggtgt ccttatagga ccagaggttg tgtttgctcc accttcttga ctcccatgtg 300
agtgtccatc tgattcagat ccatgagtgg tatgggaccc cccactgggg tggaatgtg 360
<210> 295
<211> 584
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (558)
<223> n=A,T,C or G
<400> 295
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tttacctcag tggttggcac ctggaacctg tccagggccc tcacctgact gaggagccgc 120
cgggcagtga agtaattgtc caggtctatg ctcttggggt ggataccata gccatccaag 180
gtattcctca ggttgtggaa ctgggtctga gtataggcag aactgggccc caggatgatc 240
tcccggagtg ggggaagctg tgaggtcagg taagtatcca cgtccacccg taccccaatc 300
aaactcagca gaatggtgaa ctggagaagt cetteegtta agtatttett cagagaaage 360
attgctgaag gaccagaatg tttatgcttt ttggttttta aaatcttcca aaagacaaat 420
caaggccact gctctgccgc tccagccagc aggttaccct cctcagtgtc aaaccccgta 480
ccccaccctg gcagaacaca agggatgagc tccctgacgg ccccagagga aagcacaccc 540
tgtggagcca aggccaanga cacactccag accacattca cttt
<210> 296
<211> 287
<212> DNA
<213> Homo sapiens
<400> 296
ccttatcatt cattcttagc tcttaattgt tcattttgag ctgaaatgct gcattttaat 60
tttaaccaaa acatgtctcc tatcctggtt tttgtagcct tcctccacat cctttctaaa 120
caagatttta aagacatgta ggtgtttgtt catctgtaac tctaaaagat cctttttaaa 180
ttcagtccta agaaagagga gtgcttgtcc cctaagagtg tttaatggca aggcagccct 240
gtctgaagga cacttcctgc ctaagggaga gtggtatttg cagacta
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<211> 457
 <212> DNA
 <213> Homo sapiens
 <400> 297
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ggtattaggg ataatattca tttagccttc tgagctttct gggcagactt ggtgaccttg 120
ccagctccag cagccttctt gtccactgct ttgatgacac ccaccgcaac tgtctgtctc 180
atatcacgaa cagcaaagcg acccaaaggt ggatagtctg agaagctctc aacacacatg 240
ggcttgccag gaaccatatc aacaatggca gcatcaccag acttcaagaa tttagggcca 300
 tettecaget tittaccaga aeggegatea atetiteet teageteage aaaetigeat 360
gcaatgtgag ccgtgtggca atccaataca ggggcatagc cggcgcttat ttggcctgga 420
tggttcagga taatcacctg agcagtgaag ccagacc
<210> 298
 <211> 469
 <212> DNA
 <213> Homo sapiens
<400> 298
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cagagatete aatgatteet gatteteete tteeaggagt etgaatgtet ettggtteae 120
ttccacagac tccagtggtt cttgaatttc cttttctaga ggattcattg ccccctgatt 180
tatttcttct ggagtccaca gtggtgcttg agtttctgga gatttcagtg tttccaggtt 240
ctcttgtccc gcagacttca gtgattctag gatctctgtt tctaaagatt ttactgcctc 300
tatgetetet tetttgagtg actitaagaa etettgatte teattiteaa gaggtetage 360
tatctcctgg tcaagagact tcagtggttc tagatccact ttttctgggg gtcttaatgt 420
catctgatec tgttececta gagaceteeg tegetgttga gtetetttt
<210> 299
<211> 165
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(165)
<223> n=A,T,C or G
<400> 299
tctgtggaga ggatgaggtt gagggaggtg gggtatntcg ctgctctgac cttaggtaga 60
gtcctccaca gaagcatcaa antggactgg cacatatgga ctcccttcac aggccacaat 120
gatgtgtctc tccttcgggc tggnccggta tgcacagttg gggta
<210> 300
<211> 506
<212> DNA
<213> Homo sapiens
<400> 300
tctgaggaaa gtttgggctt attagtattt gctccagcga acctccaagt tttctccatt 60
geggacaacg taactaccag etecttgget cagtggtteg cetecaetea gaagtteeca 120
gtaggttctg tcattattgt tggcacatag gccctgaata caggtgatat agggccccca 180
tgagcgctcc tccattgtga aaccaaatat agtatcattc attttctggg ctttctccat 240
cacactgagg aagacagaac catttagcac agtgacattg gtgaaatatg tttcattgat 300
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92

```
tctcacagag taattgacgg agatatatga ttgtgagtca ggaggtgtca cagttatagg 360
ctcatcagcg gagatgttga agttacctga agcagagacg caagaagagt ctttgttaat 420
atccaagaag gtctttccca tcagggcagg taagacctgg gctgcagcgt ttggattgct 480
gaatgctcct tgagaaattt ccgtga
<210> 301
<211> 304
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(304)
<223> n=A,T,C or G
<400> 301
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tgcccctttc ctctccctca gaatttgtgt ttgctgcctc tatcttgttt tttgtttttt 120
cttctggggg gggtctagaa cagtgcctgg cacatagtag gcgctcaata aatacttgtt 180
tgttgaatgt ctcctctct tttccactct gggaaaccta ngnttctgcc attctgggtg 240
accetgtatt thtttetggt geceatteea trtgneeagn taatacttee tettaaaaat 300
ctcc
                                                                   304
<210> 302
<211> 492
<212> DNA
<213> Homo sapiens
<400> 302
ttttcagtaa gcaacttttc catgctctta atgtattcct ttttagtagg aatccggaag 60
tattagattg aatggaaaag cacttgccat ctctgtctag gggtcacaaa ttgaaatggc 120
teetgtatea cataeggagg tettgtgtat etgtggcaac agggagttte ettatteaet 180
ctttatttgc tgctgtttaa gttgccaacc tcccctccca ataaaaattc acttacacct 240
cctgcctttg tagttctggt attcacttta ctatgtgata gaagtagcat gttgctgcca 300
gaatacaagc attgcttttg gcaaattaaa gtgcatgtca tttcttaata cactagaaag 360
gggaaataaa ttaaagtaca caagtccaag tctaaaactt tagtactttt ccatgcagat 420
ttgtgcacat gtgagagggt gtccagtttg tctagtgatt gttatttaga gagttggacc 480
actattgtgt gt
                                                                  492
<210> 303
<211> 470
<212> DNA
<213> Homo sapiens
<400> 303
tctggggcag caggtactcc ctacggcact agtctacagg gggaaggacg ctctgtgctg 60
gcagcggtgg ctcacatggc ctgtctgcac tgtaaccaca ggctgggatg tagccaggac 120
ttggtctcct tggaagacag gtctgatgtt tggccaatcc agtccttcag accctgcctg 180
aaacttgtat ottacgtgaa ottaaagaat aaaatgcatt totaccccga totcqcccc 240
aggactggca cgacaggccc acggcagatt agatcttttc ccagtactga tcgqtqcqtq 300
gaattccagc caccacttct gattcgattc cacagtgatc ctgtcctctq aqtattttaa 360
agaagccatt gtcaccccag tcagtgttcc aggagttggc aaccagccag tagggtgtgc 420
cattetecae tecceageee aggatgegga tggeatggae eteggeegeg
                                                                  470
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<211> 79
<212> DNA
<213> Homo sapiens
<400> 304
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gcctcttctg gtggatgcg
<210> 305
<211> 476
<212> DNA
<213> Homo sapiens
<400> 305
tcactgagcc accctacagc cagaagagat atgaggaaat tgttaaggaa gtcagcactt 60
acattaagaa aattggctac aaccccgaca cagtagcatt tgtgccaatt tctggttgga 120
atggtgacaa catgctggag ccaagtgcta acgtaagtgg ctttcaagac cattgttaaa 180
aagetetggg aatggegatt teatgettae acaaattgge atgettgtgt tteagatgee 240
ttggttcaag ggatggaaag tcacccgtaa ggatggcaat gccagtggaa ccacgctgct 300
tgaggctctg gactgcatcc taccaccaac tcgtccaact gacaagccct tgcgcctgcc 360
tctccaggat gtctacaaaa ttggtggtaa gttggctgta aacaaagttg aatttgagtt 420
gatagagtac tgtctgcctt cataggtatt tagtatgctg taaatatttt taggta 480
<210> 306
<211> 404
<212> DNA
<213> Homo sapiens.
<400> 306
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tcacagaaac tacagaagtc aggacccagg cgaggacctc aggaacaagt gccccctgca 120
gacagagaga cgcagtagca acagcttctg aacaactaca taataatgcg gggagaatcc 180
tgaagaccac tgcatcccac aagcactgac aaccacttca ggattttatt tcctccactc 240
taacccccag atccatttat gagaagtgag tgaggatggc aggggcatgg agggtgaagg 300
gacagcaagg atggtctgag ggcctggaaa caatagaaaa tcttcgtcct ttagcatatc 360
ctggactaga aaacaagagt tggagaagag gggggttgat acta
<210> 307
<211> 260
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(260)
<223> n=A,T,C or G
<400> 307
tectgeetan acatetgtga gggeeteaag ggetgetgee tegaetttet eeetagetaa 60
gtccacccgt ccagggacac agccagggca ctgctctgtg ctgacttcca ctgcagccaa 120
gggtcaaaat gaagcatctg cggaggccag gactccttgg catcggacac agtcagggga 180
aaagccaccc tgactctgca ggacagaggg tctagggtca tttggcagga gaacactggt 240
gtgccaaggg aagcnancat
                                                                   260
```

<210> 308

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<211> 449
<212> DNA
<213> Homo sapiens
<400> 308
totgtgctcc cgactcctcc atctcaggta ccaccgactg cactgggcgg ggccctctgg 60
ggggaaaggc tccacggggc agggatacat ctcgaggcca gtcatcctct ggaggcagcc 120
caatcaggtc aaagattttg cccaactggt cggcttcaga gtttccacag aagagaggct 180
ttcgacgaaa catctctgca aagatacagc caacactcca catgtccaca ggtgttgcat 240
atgtggactg cagaagaact tcgggagctc ggtaccagag tgtaacaacc ttgatcgttt 300
cggctggcaa gcctggtggg ggtgccttgt ccagatatgt ccttaggtcc tggtctacat 360
gctcaaacac cagggttacc ttgatctccc ggtcagttcg ggatgtggca cagacgtcca 420
tcagccggac aacattggga tgctcaaaa
<210> 309
<211> 411
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (384)
<223> n=A,T,C or G
<400> 309
ctgtggaaac ctggggtgcc gggtaaatgg agaactccag cttggatttc ttgccataat 60
caactgagag acgttccatg agcagggagg tgaacccaga accagttccc ccaccaaagc 120
tgtggaaaac caagaagccc tgaagaccgg tgcactggtc agccagcttg cgaattcqqt 180
ccaacacaag gtcaatgatc tccttgccaa tggtgtagtg ccctcgggca tagttattgg 240
cagcatette ettgeetgtg atgagetget cagggtggaa gagetggegg taggtgecag 300
tgcgaacttc atcaatgact gtgggttcca agtctacaaa cacagcccgg ggcacgtgct 360
tgccagcgcc cgtctcactt gaanaagggt gtttgaagga agtcatctcc t 420
<210> 310
<211> 320
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (250)
<223> n=A,T,C or G
<400> 310
tectegteca gettgacteg attagtecte ataaggtaag caaggeagat ggtggetgac 60
cgggaaatgc ctgcctggca qtgqacaaac accetteete caqeattett qatqqaqtet 120
atgaagtcaa tggcctcgtt gaaccaggag ctgatgtctg ccttgtggtt gtcctccaca 180
gggatgctct tgtactggta gtgaccctca aaatggttgg gacaattggc tgagacgttg 240
atcaaggcan ttatgcccaa ggcatccagc atgtccttgc gggaagcgtg atacgcactg 300
cccaggtaca gaaagggcag
<210> 311
<211> 539
<212> DNA
<213> Homo sapiens
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PCT/US00/05308

```
<400> 311
tetggeceat gaagetgaag ttgggagaga tgatgetteg cetetgette acaaacteaa 60
aggcctcgtc cagcttgact cgattagtcc tcataaggta agcaaggcag atggtggctg 120
accgggaaat gcctgcctgg cagtggacaa acacccttcc tccagcattc ttgatggagt 180
ctatgaagtc aatggcctcg ttgaaccagg agctgatgtc tgccttgtgg ttgtcctcca 240
cagggatgct cttgtactgg tagtgaccct caaaatggtt gggacaattg gctgagacgt 300
tgatcaaggc agttatgccc aaggcatcca gcatgtcctt gcgggaagcg tgatacgcac 360
tgcccaggta cagaaagggc aggatttcca ccgggccacc ctgaaatcca gaaatatcca 420
acattcatca agcttgctca aagccaaggc cagtgcccat acccacaaaa actttctgct 480
ggaaaagtca atttcagata ccgagtgaac tcagttctgt tgctggagga taaataaat 540
<210> 312
<211> 475
<212> DNA
<213> Homo sapiens
<400> 312
tcaaggatct tcctaaagcc accatgtgag aggattcgga cgagagtctg agctgtatgg 60
cagaccatgt cctgctgttc tagggtcatg actgtgtgta ctctaaagtt gccactctca 120
caggggtcag tgatacccac tgaacctggc aggaacagtc ctgcagccag aatctgcaag 180
cagegeetgt atgeaacgtt tagggeeaaa ggetgtetgg tggggttgtt cateacagea 240
taatggccta gtaggtcaag gatccagggt gtgaggggct caaagccagg aaaacgaatc 300
ctcaagtcct tcagtagtct gatgagaact ttaactgtgg actgagaagc attttcctcg 360
aaccageggg catgteggat ggetgetaag geactetgea ataetttgat atccaaatgg 420
agttctggat ccagttttcg aagattgggt ggcactgttg taatgagaat cttca 480
<210> 313 .
<211> 456
<212> DNA
<213> Homo sapiens
<400> 313
tccacttaaa gggtgcctct gccaactggt ggaatcatcg ccacttccag caccacgcca 60
agcctaacat cttccacaag gatcccgatg tgaacatgct gcacgtgttt gttctgggcg 120
aatggcagcc catcgagtac ggcaagaaga agctgaaata cctgccctac aatcaccagc 180
acgaatactt cttcctgatt gggccgccgc tgctcatccc catgtatttc cagtaccaga 240
teateatgae catgategte cataagaaet gggtggaeet ggeetgggee gteagetaet 300
acatccggtt cttcatcacc tacatccctt tctacggcat cctgggagcc ctccttttcc 360
tcaacttcat caggttcctg gagagccact ggtttgtgtg ggtcacacag atgaatcaca 420
tcgtcatgga gattgaccag gaggacctcg gcccgc
<210> 314
<211> 477
<212> DNA
<213> Homo sapiens
<400> 314
tgcgtgggct tctggaagcc tggatctgga atcattcacc agattattct ggaaaactat 60
gcgtaccctg gtgttcttct gattggcact gactcccaca cccccaatgg tggcggcctt 120
gggggcatct gcattggagt tgggggtgcc gatgctgtgg atgtcatggc tgggatcccc 180
tgggagctga agtgccccaa ggtgattggc gtgaagctga cgggctctct ctccggttgg 240
tecteaceca aagatgtgat cetgaaggtg geaggeatec teaeggtgaa aggtggeaca 300
ggtgcaatcg tggaatacca cgggcctggt gtagactcca tctcctgcac tggcatggcg 360
acaatctgca acatgggtgc agaaattggg gccaccactt ccgtgttccc ttacaaccac 420
```

```
aggatgaaga agtatctgag caagaccggc cgggaagaca ttgccaatct agctgat
                                                                  477
<210> 315
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A,T,C \text{ or } G
<400> 315
caggiactgg atgicaggic tgcgaaacti citanattit gaccicagic cataaaccac 60
actatcacct eggecateat atgtgtetac tgtggggaca actggagtga aaactteggt 120
tgctgcaggt ccgtgggaaa atcagtgacc agttcatcag attcatcaga atggtgagac 180
tcatcagact ggtgagaatc atcagtgtca tctacatcat cagagtcgtt cgagtcaatg 240
<210> 316
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 316
nttntgtgat agtgtggttt atggactgag gncaaaatnt aagaagtttc gcagacctga 60
catecaance tgeeegngeg gnegetegaa aggnegaatt etgeagatat ceateacact 120
ggcggccgct cgagcatgca tctagagggc ccaattcgcc ctatantgag tnatattaca 180
attcactggc cgtcnnttta caacgtcgtg actgggaaaa ccctggcgtt acccaactta 240
<210> 317
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
\langle 223 \rangle n = A,T,C or G
<400> 317
aggtaccetg eccancagee tgggngeetg ggttgtetee ttgteeatee actggteeat 60
totgototgo attittitgt tootottitig gaggitocac titigggitig ggottigaaa 120
ttatagggct acaantacct cggccgaaac cacnctaagg gcgaattctg cagatatcca 180
teacactggc ggnegetega geatgeatet agagggeeca attegeecta tagtgagteg 240
<210> 318
<211> 241
```

```
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 318
cgngnacaan ntacattgat gganggtntg nggntctgan tntttantta cantggagca 60
ttaatatttt cttnaacgtn cctcaccttc ctgaantaaa nactctgggt tgtagcgctc 120
tgtgctnana accaentnaa etttacatee etettttgga ttaateeact gegeggeeac 180
ctctgccgcg accacgctaa gggcnaattc tgcagatatc catcacactg gcggccgctc 240
<210> 319
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 319
caggtactga tcggtgcgtg gaantccagc caccanttnt gattcgattc cacagtgatc 60
ctgtcctctg agtattttaa agaagccatt gtcaccccag tcagtgttcc aggagttggc 120
aaccagccag tagggtgtgc cattetecae teeccageee aggatgegga tggcatggce 180
acceateate teteeggtga egtgttggta eeteggeege gaceaegeta agggegaatt 240
<210> 320
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
\langle 223 \rangle n = A,T,C or G
<400> 320
ggcaggtacc aacagagctt agtaatntct aaaaagaaaa aatgatcttt ttccgacttc 60
taaacaagtg actatactag cataaatcat tctagtaaaa cagctaaggt atagacattc 120
taataatttg ggaaaaccta tgattacaag tgaaaactca gaaatgcaaa gatgttggtt 180
ttttgtttct cagtctgctt tagcttttaa ctctnnnaan cncatgcaca cttgnaactc 240
<210> 321
<211> 241
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 321
angtaccaac agagettagt aattnntaaa aagaaaaaat gatetttte egaettetaa 60
acaagtgact atactagcat aaatcattct agtaaaacag ctaaggtata gacattctaa 120
taatttggga aaacctatga ttacaagtga aaactcagaa atgcaaagat gttggttttt 180
tgtttctcag tctgctttag cttttaactc tggaagcgca tgcacacntg aactctqctc 240
<210> 322
<211> 241
<212> DNA
<213> Homo sapiens
<400> 322
ggtaccaaca gagcttagta atttctaaaa agaaaaaatg atctttttcc gacttctaaa 60
caagtgacta tactagcata aatcattctt ctagtaaaac agctaaggta tagacattct 120
aataatttgg gaaaacctat gattacaagt aaaaactcag aaatgcaaag atgttggttt 180
tttgtttctc agtctgcttt agcttttaac tctggaagcg catgcacact gaactctgct 240
<210> 323
<211> 241
<212> DNA
<213> Homo sapiens `
<400> 323
cgaggtactg tcgtatcctc agccttgttc tatttcttta ttttagcttt acagagatta 60
ggtctcaagt tatgagaatc tccatggctt tcaggggcta aacttttctg ccattcttt 1.20
getettaccg ggeteagaag gacatgteag gtgggatacg tgtttetett teagagetga 180
agaaagggtc tgagctgcgg aatcagtaga gaaagccttg gtctcagtga ctccttqqct 240
<210> 324
<211> 241
<212> DNA
<213> Homo sapiens
<400> 324
aggtactgtc gtatcctcag ccttgttcta tttctttatt ttagctttac agagattagg 60
totcaagtta tgagaatoto catggottto aggggotaaa ottttotgoo attottttgc 120
tcttaccggg ctcagaagga catgtcaggt gggatacgtg tttctctttc agagctgaag 180
aaagggtctg agctgcggaa tcagtagaqa aagccttggt ctcagtgact ccttqqcttt 240
<210> 325
<211> 241
<212> DNA
<213> Homo sapiens
<400> 325
ggcaggtaca titgtitigc ccagccatca cictititig tgaggagcct aaatacattc 60
tteetggggt ccagagteee catteaagge agteaagtta agacactaae ttggeeettt 120
```

```
cctgatggaa atatttcctc catagcagaa gttgtgttct gacaagactg agagagttac 180
atgttgggaa aaaaaaagaa gcattaactt agtagaactg aaccaggagc attaagttct 240
<210> 326
<211> 241
<212> DNA
<213> Homo sapiens
<400> 326
gcaggtacat ttgttttgcc cagccatcac tcttttttgt gaggagccta aatacattct 60
tcctggggtc cagagtcccc attcaaggca gtcaagttaa gacactaact tggccctttc 120
ctgatggaaa tatttcctcc atagcagaag ttgtgttctg acaagactga gagagttaca 180
tgttgggaaa aaaaagaagc attaacttag tagaactgat ccaggagcat taagttctga 240
                                                                  241
<210> 327
<211> 241
<212> DNA
<213> Homo sapiens
<400> 327
ggtaccagac caagtgaatg cgacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacagtata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tgattatcag 240
                                                                   241
<210> 328
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)..
<223> n = A,T,C or G
<400> 328
ggtacnagac caaatgaang ccacagggaa ttatttcctg tgttgataat tcatgaagta 60
gaacantata atcaaaatca attgtatcat cattagtttt ccactgcctc acactagtga 120
gctgtgccaa gtagtagtgt gacacctgtg ttgtcatttc ccacatcacg taagagcttc 180
caaggaaagc caaatcccag atgagtctca gagagggatc aatatgtcca tnatcatcan 240
g
                                                                  241
<210> 329
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
```

```
<400> 329
 ttcaggtcga grtggcrgca gattrgrggt gcnttctgag ccgrctgrcc rgcgccaaaa 60
ngcttcaaag tattattaaa aacatatgga tccccatgaa gccctactac accaaagttt 120
accaggagat ttggatagga atggggctga tgggcttcat cgtttataaa atccgggctg 180
ctgataagaa gtaaggcttt gaaagcttca gcgcctgctn ctggtcanna ctaaccatan 240
<210> 330
<211> 241
<212> DNA
<213> Homo sapiens
<400> 330
ttttgtgcag atttgtggtg cgttctgagc cgtctgtcct gcgccaagat gcttcaaagt 60
attattaaaa acatatggat ccccatgaag ccctactaca ccaaagttta ccaggagatt 120
tggataggaa tggggctgat gggcttcatc gtttataaaa tccgggctgc tgataaaaqa 180
agtaaggctt tgaaagcttc agcgcctgct cctggtcatc actaaccaga tttacttgga 240
<210> 331
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 331
nttttaggna ctttgggctc cagacttcac tggtcttagg nattgaaacc atcacctggn 60
ntgcattcct catgactgag gttaacttaa aacaaaaatg gtaggaaagc tttcctatnc 120
ttcnggtaag anacaaatnt nctttaaaaa aangtggaag gcatgacnta cgtgagaact 180
gcacaaactg gccactgaca aaaatgaccc ccatttgtgt gacttcattg agacacatta 240
<210> 332
<211> 241
<212> DNA
<213> Homo sapiens
<400> 332
tgtgaggaga gggaacatgc tgagaaactg atgaagctgc agaaccaacg aggtggccga 60
atcttccttc aggatatcaa gaaaccagac tgtgatgact gggagagcgg gctgaatgca 120
atggagtgtg cattacattt ggaaaaaaat gtgaatcagt cactactgga actgcacaaa 180
ctggccactg acaaaaatga cccccatttg tgtgacttca ttgagacaca ttacctgaat 240
                                                                   241
<210> 333
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```

```
<222> (1)...(241)
<223> n = A.T.C or G
<400> 333
caggracaag ctttttttt ttttttttt ttttttttt ttgnaaatac tntttattgn 60
aaatattcta tcctaaattc catatagcca attaattntt acanaatntt ttgttaattt 120
ttgngngtat aaattttaca aaaataaagg gtatgtttgt tgcacacaac ttacaaataa 180
taataaactn tttattgnaa atattnttta ttgnaaatat tctttatcct aaattccata 240
<210> 334
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 334
tacctgctgn aggggntgaa gnentetetg etgeeceagg catetgeane ceetgetget 60
ggttctgccc ctgctgcagc agaggagaag aaagatgaga agaaggagga gtctgaagag 120
tcagatgatg acatgggatt tggccttttt gattaaannc ctgctcccct gcaaataaag 180
241
<210> 335
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 335
ctatgtgctg ggatgactat ggagacccaa atgtctcana atgtatgtcc cagaaacctg 60
tggctgcttc aaccattgac agttttgctg ctgctggctt ctgcagacag tcaagctgca 120
gctcccccaa aggctgtgct gaaacttgag cccccgtgga tcaacgtgct ccaggaggac 180
tctgtgactc tgacatgcca gggggctcgc agccctgaga gcgactccat tcagtggttc 240
<210> 336
<211> 241
<212> DNA
<213> Homo sapiens
<400> 336
taccaaccta tgcagccaag caacctcagc agttcccatc aaggccacct ccaccacaac 60
cgaaagtatc atctcaggga aacttaattc ctgcccgtcc tgctcctgca cctcctttat 120
atagttccct cacttgattt ttttaacctt ctttttgcaa atgtcttcag ggaactgagc 180
taatactitt tittitcitg atgittictt gaaaageett teigtigeaa etaigaatga 240
```

102

```
<210> 337
 <211> 241
 <212> DNA
<213> Homo sapiens
 <220>
 <221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 337
ggtactgtat gtagctgcac tacaacagat tcttaccgtc tccacanagg tcatanattg 60
taaatggtna atactgactt tttttttatt cccttgactc aagacagcta acttcatttt 120
cagaactgtt ttaaaccttt gtgtgctggt ttataaaata atgtgtgtaa tccttgttgc 180
tttcctgata ccagactgtt tcccgtggtt ggttagaata tattttgntt tgatgcttat 240
<210> 338
<211> 241
<212> DNA
<213> Homo sapiens
<400> 338
aggtacaggt gtgcgctgag ccgagtttac acggaaagga taaagcccat ttagtttctt 60
ctcaaatgga gttttccact ttcctttgaa gtagacagca ttcaccagga tcatcctggt 120
atccccatct acagaacctt caggtaacaa gtttgggatt ttgcctttgg tttgagtctt 180
gacccaggaa ttaatctttt ttctagcttc ttctgcacat tctaggaagt ctactgcctg 240
<210> 339
<211> 241
<212> DNA
<213> Homo sapiens
<400> 339
taccgacggc tcctggaggg agagagtgaa gggacacggg aagaatcaaa gtcgagcatg 60
adagtgtctg caactccaaa gatcaaggcc ataacccagg agaccatcaa cggaagatta 120
gttctttgtc aagtgaatga aatccaaaag cacgcatgag accaatgaaa gtttccgcct 180
gttgtaaaat ctattttccc ccaaggaaag tccttgcaca gacaccagtg agtgagttct 240
<210> 340
<211> 241
<212> DNA
<213> Homo sapiens
<400> 340
gtagccctca cacacacatg cccgtaacag gatttatcac aagacacgcc tgcatgtaga 60
ccagacacag ggcgtatgga aagcacgtcc tcaagactgt agtattccag atgagctgca 120
gatgettace taccaeggee gtetecacca gaaaaccate gecaacteet gegateaget 180
tgtgacttac aaaccttgtt taaaagctgc ttacatggac ttctgtcctt taaaagcttc 240
С
                                                                   241
```

<210> 341

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<211> 241
 <212> DNA
 <213> Homo sapiens
 <400> 341
 gtaccgccta ctttcgtctc atgtctccga acttcttgct gatggccgtt ccaacgttgc 60
 tgaaagctgc agttgccttt tgccctgcgt gactcagggt ttcatgtgtt ttcttgtagg 120
 cagtggtagt ctgcatgtca tgccagcttt tgctgaagtt ctgttttaat tcattcatca 180
ggttcatgcc gagttttgtt ttatctcaac tagatgcctt tctttcgctg acaaaacttg 240
t
<210> 342
<211> 241
<212> DNA
<213> Homo sapiens
<400> 342
gtacattggt gctataaata taaatgctac ttatgaagca tgaaattaag cttcttttt 60
cttcaagttt tttctcttgt ctagcaatct gttaggcttc tgaaccaaga ccaaatgttt 120
acgttcctct gctgcatacc aacgttactc caaacaataa aaatctatca tttctgctct 180
gtgctgagga atggaaaatg aaacccccac cccctgaccc ctaggactat acagtggaaa 240
<210> 343
<211> 241
<212> DNA
<213> Homo sapiens
<400> 343
gtacatgtgg tagcagtaat ttttttgaag caactgcact gacattcatt tgagttttct 60
ctcattatca gattctgttc caaacaagta ttctgtagat ccaaatggat taccagtgtg 120
ctacagactt cttattatag aacagcattc tattctacat caaaaatagt ttgtgtaagt 180
tagttttggt taccatctaa aatattttta aatgttcttt acataaaaat ttatgttgtg 240
t
                                                                   241
<210> 344
<211> 241
<212> DNA
<213> Homo sapiens
<400> 344
ggtacaaaat tgttggaatt tagctaatag aaaaacatag taaatattta caaaaacgtt 60
gataacatta ctcaagtcac acacatataa caatgtagac aggtcttaac aaagtttaca 120
aattgaaatt atggagattt cccaaaatga atctaatagc tcattgctga gcatggttat 180
caatataaca tttaagatct tggatcaaat gttgtccccg agtcttctgc aatccagtcc 240
<210> 345
<211> 241
<212> DNA
<213> Homo sapiens
<400> 345
ggtacgaagc tgagcgcacg ggggttgccc cagcgtggag cctggacctc aaacttcacg 60
gaaaatgctc tctctcttg acaggcttcc agctgtctcc taatttcctg gatgaactct 120
```

```
ccccggcgat ttaactgatc ctgaaaagtg gtgagaggac tgaggaagac aaccaggtca 180
gcgttagatc ggcctctgag ggtggtgccc ttgcctgagg agccaccctt taccaccttg 240
g
<210> 346
<211> 241
<212> DNA
<213> Homo sapiens
<400> 346
caggtaccac tgagcctgag atggggatga gggcagagag aggggagccc cctcttccac 60
teagttgttc ctactcagac tgttgcactc taaacctagg gaggttgaag aatgagaccc 120
ttaggtttta acacgaatcc tgacaccacc atctataggg tcccaacttg gttattgtag 180
gcaaccttcc ctctctcctt ggtgaagaac atcccaagcc agaaagaagt taactacagt 240
g
<210> 347
<211> 241
<212> DNA
<213> Homo sapiens
<400> 347
aggtacatct aaaggcatga agcactcaat tgggcaatta acattagtgt ttgttctctg 60
atggtatctc tgagaatact ggttgtagga ctggccagta gtgccttcgg gactgggttc 120
acceccaggt etgeggeagt tgteacageg erageceege tggeeteeaa ageatgtgea 180
ggagcaaatg gcaccgagat attecttetg ceactgttet cetacgtggt atgtetteec 240
а
<210> 348
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 348
angtacttgg caagattnga tgctcttgng ctcantgaca tcattcataa cttgtnngtg 60
tgancagagg aggagnneat catentgtee teattegtea gnnnectete etetetgaat 120
ctcaaacaag ttgataatgg agaaaaattt gaattctcag gattgaggct ggactggttc 180
egectacang catacactag egtggetaag geceetetge accetgeatg anaaccetga 240
<210> 349
<211> 241
<212> DNA
<213> Homo sapiens
<400> 349
gcaggtacca tttgtctgac ctctgtaaaa aatgtgatcc tacagaagtg gagctggata 60
atcagatagt tactgctacc cagagcaata tctgtgatga agacagtgct acagagacct 120
gctacactta tgacagaaac aagtgctaca cagctgtggt cccactcgta tatggtggtg 180
agaccaaaat ggtggaaaca gccttaaccc cagatgcctg ctatcctgac taatttaagt 240
```

```
241
<210> 350
<211> 241
<212> DNA
<213> Homo sapiens
<400> 350
aggtactgtg gatatttaaa atatcacagt aacaagatca tgcttgttcc tacagtattg 60
cgggccagac acttaagtga aagcagaagt gtttgggtga ctttcctact taaaattttg 120
gtcatatcat ttcaaaacat ttgcatcttg gttggctgca tatgctttcc tattgatccc 180
aaaccaaatc ttagaatcac ttcatttaaa atactgagcg gtattgaata cttcqaaqca 240
                                                                   241
<210> 351
<211> 241
<212> DNA
<213> Homo sapiens
<400> 351
tacagaaatc atttggagcc gttttgagac agaagtagag gctctgtcaa gtcaatactg 60
cattgcagct tggtccactg aagaagccac gcctgagata caaaagatgc actacacttg 120
accegettta tgttegette eteteceett eteteteate aactttatta ggttaaaaca 180
CCaCatacag getteetcca aatgacteee tatgtetggg gtttggttag aattttatge 240
C
<210> 352
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 352
gtaccetgtn gagetgeace aagattannt ggggeeatea tgactgeane caenacgang 60
acgcaggcgt gnagtgcatc gtctgacccg gaaacccttt cacttctctq ctcccqagqt 120
gtcctcnggc tcatatgtgg gaaggcanan gatctctgan gagttncctg gggacaactg 180
ancagcotot ggagagggg cattaataaa gotoaacato attggcaaaa aaaaaaaaaa 240
<210> 353
<211> 241
<212> DNA
<213> Homo sapiens
<400> 353
aggtaccagt gcattaattt gggcaaggaa agtgtcataa tttgatactg tatctqtttt 60
ccttcaaagt atagagcttt tggggaagga aagtattgaa ctgggggttg gtctggccta 120
ctgggctgac attaactaca attatgggaa atgcaaaagt tgtttggata tggtagtgtg 180
tggttctctt ttggaatttt tttcaggtga tttaataata atttaaaaact actataaaaa 240
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<210> 354 <211> 241 <212> DNA <213> Homo sapiens <220> <221> misc_feature <222> (1)...(241) <223> n = A,T,C or G <400> 354 ngcaggtccg ggcaggtacc aagattcatt ctcatcaaaa actagaaaca gaagggcaaa 60 ttccagtttc cttctgggat tgaatacttt caagtaaggt cttcgacaaa caatcagggg 120 gccaattaat ccactgtaga ggtccttaac ttgatccaca gttgaataat aagcccatgg 180 aatacaagca gaatcetetg ttecagetee agatetttet gggattttee atacgtaagt 240 <210> 355 <211> 241 <212> DNA <213> Homo sapiens <400> 355 ggtacccacc ctaaatttga actcttatca agaggctgat gaatctgacc atcaaatagg 60 ataggatgga collittitg agticatigt ataaacaaat titotgatti ggacttaati 120 cocaaaggat taggtotact cotgotoatt cactotttca aagototgto cactotaact 180 tttctccagt gtcatagata gggaattgct cactgcgtgc ctagtctttc ttcacttacc 240 <210> 356 <211> 241 <212> DNA <213> Homo sapiens <220> <221> misc_feature <222> (1)...(241) <223> n = A,T,C or G<400> 356 aggtactgta attgagcatc cggaatntgg agaagtaatt tagctacagg gtgaccaacg 60 caagaacata tgccagttcc tcgtagagat tggactggct aaggacgatc agctgaaggt 120 tcatgggttt taagtgcttg tggctcactg aagcttaagt gaggatttcc ttgcaatgag 180 tagaatttcc cttctcccc ttgtcacagg tttaaaaacc tcacagcttg tataatgtaa 240 <210> 357 <211> 241 <212> DNA <213> Homo sapiens <400> 357 ttttgtacca ccgatatgat caaggaaaat tctgcccatt tttatggctg aagttctaaa 60 aacctaattc aaagttcttc catgatccta cactgcctcc aagatggtcc aggctggcat 120

aaggcctgag cggcggtgag atccgcggct gccagcagct tgtcgctctt cagctggtat 180

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gaagcccctc ggccacccga gtctccagga cctgcccggg cgccgctcga aagggcgaat 240
t
 <210> 358
 <211> 241
 <212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 358
aggtacgggg agtggggtg aagcntgttc tctacatagg caacacagcc gcctaantca 60
caaagtcagt ggtcggccgc ttcgaccaac atgtggtgag cattccacgg gcgcatgaag 120
tctgggtgct gtgctcgagt ctctgaatat tttgatagga agcgacaaga aaattcaaac 180
tgctctttgc tgactactgg aaagtgaaaa gatgctcaag tttaccattc aaagaaacca 240
<210> 359
<211> 241
<212> DNA
<213> Homo sapiens
<400> 359
gaggtacaca aaaggaatac cttctgagag ccagggagtg aggaaagggg aaggagactt 60
gacgtcaagg gtgcttttga ggaacatgac gggccagcca gcctgcccca actttqaggc 120
cctgctgggc tcttgtgact ataaatatac tgtctatttc taatgcaatc cgtctttcct 180
gaaagatett gttatetttt actattgaga catgetttea tttttgtggt cetgttteca 240
а
<210> 360
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
\langle 223 \rangle n = A,T,C or G
<400> 360
ngtactctat actaattctg cctttttata cttaattcta aatttctccc ctctaattta 60
caacaaattt tgtgattttt ataagaatct atgcctcccc aattctcaga ttcttctctt 120
ttctccttta tttctttgct taaattcagt ataagctttc ttggtatttt aggcttcatg 180
cacattetta tteetaaaca eeageagtte tteagagaee taaaateeag tataggaata 240
<210> 361
<211> 241
<212> DNA
<213> Homo sapiens
<400> 361
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aggtactete egtgeecega caetgaacat tatecageca gatetgeeca gtgeeagete 60
ccactttgta cttttcttac tatcctgtct agaatcatgt cttatgattt taacagatat 120
agaaccactc ctagaaaatg ttctttcact ttctcgtttc ctttttaatc tatcatcctg 180
<210> 362
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 362
aggtactttt ataccingci tangicagig acagatttac caaigacaac acaatttaa 60
aattccaaca catatattac tttgtcctat gaagggcaaa aagtcaatat attttaaatt 120
ttaaaaacag aatggatata atgacctttt tacacatcag tgatatttaa aagacttaaa 180
gagacaatac tatggttgag acactggctt cctattccag ccctaattaa agaaaaaata 240
<210> 363
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 363
ttangtacta aaaacaaaat cctaattctg ttttaaagag ctgggagatg ttaatcatat 60
gctcagtttt tccacgttat aatttcctaa atgcaaactt ttcaatcagg gcagttcaaa 120
ttcattacat cacagtaaat aacagtagcc aactttgatt ttatgcttat aggaaaaaaa 180
atcctgtaga tataaaaaca gcaaattttg acaaataaaa ctcaaaccat tcatccctaa 240
<210> 364
<211> 241.
<212> DNA
<213> Homo sapiens
<400> 364
ggtacaagca gttagtcctg aaggcccctg ataagaatgt catcttctcc ccactgagca 60
tetecacege ettggeette etgtetetgg gggeecataa taceaecetg acagagatte 120
tcaaaggcct caagttcaac ctcacggaga cttctgaggc agaaattcac cagagcttcc 180
agcacctcct gegeaccctc aatcagteca gegatgaget geagetgagt atgggaaatg 240
С
                                                                241
<210> 365
<211> 241
<212> DNA
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<213> Homo sapiens
 <400> 365
cgaggtactg agattacagg catgagccac cacgcccggc caaaaacatt taaaaaatga 60
ctgtccctgc tcaaatactg cagtaggaaa tgtaatttga catatatcac ttccagaaaa 120
aaactttaaa tctttctata aaatgaattt gatacatcat cagcatgaag tgaagttaaa 180
attitettaca aagtaaatte aggtatatea acaatgagat ecaaaagtat eggtteaaga 240
<210> 366
<211> 241
<212> DNA
<213> Homo sapiens
<400> 366
ggcaggtaca catcaaacac ttcattgcct aaatgcaggg acatgcttcc atctgaccac 60
ttgactatcc gagcattgct ttctttaatt tcatttcctt cttcatctcg gcgtatcctc 120
catcttatag tattttctac ctttaatttt aacctggttc taccttcttc atccagcatt 180
tetteatett caaatteate tteataatae tgggetetae aettgagaaa gttgggeagt 240
<210> 367
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 367
gcaggtacaa ataattcctg ttgtnacatt tagtggacgc gattatctgt atacctcaaa 60
ttttaattta agaaagtate aettaaagag cateteattt tetatagatt gaggettaat 120
tactgaaaag tgactcaacc aaaaagcaca taacctttta aaggagctac acctaccgca 180
gaaagtcaga tgccctgtaa ataactttgg tctttcaaaa tagtggcaat gcttaagata 240
<210> 368
<211> 241
<212> DNA
<213> Homo sapiens
<400> 368
tttgtacatt gttaatagtg accctcggag gaaatggatt tctcttctat taaaaactct 60
atggtatata agcattacat aataatgcta cttaaccacc ttttgtctca agaattatca 120
ccaaagtttt ctggaaataa gtccacataa gaattaaata tttaaaaggt gaaatgttcc 180
ttattttaac tttagcaaga tcttttcttt ttcattaaga aacactttaa taattttaaa 240
g
<210> 369
<211> 241
<212> DNA
<213> Homo sapiens
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<400> 369
gcaggtactt tattcttatt tcttatccta tattctgtgt tacagaaaaa ctactaccat 60
aaacaaaaca ccaaccagcc acagcagttg tgtcaagcat gacaattggt ctagtcttca 120
cattttatta gtaagtctat caagtaagag atgaagggtc tagaaaacta gacacaaagc 180
aaccagggtc caaatcacca aggtagatct gtgcttagct aaagggaaac acccgaagat 240
<210> 370
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 370
ngttcacagt gccctccgg cctcgccatg aggctcttcc tgtcgctccc ggtcctggtg 60
gtggttctgt cgatcgtctt ggaaggccca gccccagccc aggggacccc agacgtctcc 120
agtgccttgg ataagctgaa ggagtttgga aacacactgg aggacaaggc tcgggaactc 180
atcagccgca tcaaacagag tgaactttct gccaagatgc gggagtggtt ttcagaagac 240
<210> 371
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 371
ggcaggtcat cttgagcctt gcacatgata ctcagattcc tcacccttgc ttaggagtaa 60
aacaatatac tttacagggt gataataatc tccatagtta tttgaagtgg cttgaaaaag 120
gcaagattga cttttatgac attggataaa atctacaaat cagccctcga gttattcaat 180
gataactgac aaactaaatt atttccctag aaaggaagat gaaaggnagt ggagtgtggt 240
<210> 372
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 372
aggtacagca aagcgaccct tggtgnnata gatcagacgg aaattctctc ccgtcttgnc 60
aatgctgatg acatccatga atccagcagg gtaggttata tcagttcgga ccttgccatc 120
gattttaatg aaccgctgca tgcaaatcit ctttacttca tctcctgtca gggcatactt 180
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aagtotgtto otcaggaaaa tgatgagggg gagacactot otcaacttgt ggggaccggt 240
<210> 373
<211> 241
<212> DNA
<213> Homo sapiens
<400> 373
tactgaaaca gaaaaaatgt attcccacaa aagctgttac acagcggttt cccqtcccca 60
gaagcagtag aaaatcttag cattccaatg gaaggcatgt atttgtaaaa tattctaaaa 120
tragetetat agettecettg tertetttga taagggatea garagagggt gegereere 180
tcagcagcta cccttcttga caaactggtc tccaataata cctttcagaa acttacaaga 240
<210> 374
<211> 241
<212> DNA
<213> Homo sapiens
<400> 374
caggiactaa aacttacaat aaatatcaga gaagccgita giittitacag caicgicigc 60
ttaaaagcta agttgaccag gtgcataatt tcccatcagt ctgtccttgt agtaggcagg 120
gcaatttctg ttttcatgat cggaatactc aaatatatcc aaacatcttt ttaaaacttt 180
gatttatagc tcctagaaag ttatgttttt taatagtcac tctactctaa tcaggcctag 240
<210> 375
<211> 241
<212> DNA
<213> Homo sapiens
<400> 375
aggtacaaag gaccagtatc cctacctgaa gtctgtgtgt gagatggcag agaacgqtqt 60
gaagaccatc acctccgtgg ccatgaccag tgctctgccc atcatccaga agctagagcc 120
gcaaattgca gttgccaata cctatgcctg taaggggcta gacaggattg aggagagact 180
gcctattctg aatcagccat caactcagat tgttgccaat gccaaaggcg ctgtgactgg 240
<210> 376
<211> 241
<212> DNA
<213> Homo sapiens
<400> 376
ggtacatttt actttccttc tttcagaatg ctaataaaaa acttttgttt atacttaaaa 60
aaaccataaa tcagacaaac aaaagaaacg attccaacat cacttctgtq atgagaaaaq 120
aggcaatgga attcaacata agcaaagaaa actctacctg gaggaaagaa atcgatcagc 180
gaagaaacaa ctcggggctg ctgccagact gcaggccatg cgaggaggag cctcctagag 240
<210> 377
<211> 241
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 377
tectttetgt ccaggtgatt cacagactag acetttetta tecteeteet agagttttga 60
cttgggactc tagtgttaag atgatgagcc cgtgcatcag gtccttctgc actttggtgg 120
aagteteeca gggtaggttt eetatttgaa acagtggaat catgttteea gtgataaagt 180
ttaatgacct catcetttt ttttttttc tcatctgcca tttgtgtgtc ttanatgggt 240
<210> 378
<211> 241
<212> DNA
<213> Homo sapiens
<400> 378
aggtcagcga tcaggtcctt tatgggcagc tgctgggcag ccccacaagc ccagggccag 60
ggcactatct ccgctgcgac tccactcagc ccctcttggc gggcctcacc cccagcccca 120
agtectatga gaacetetgg ttecaggeea geceettggg gaceetggta acceeageee 180
caagecagga ggacgactgt gtctttgggc cactgetcaa etteeceete etgeagggga 240
<210> 379
<211> 241
<212> DNA
<213> Homo sapiens
<400> 379
tacggagcaa tcgaagaggc atatccacac ttggggtggc tatagggctg gaaaatqctq 60
aagatgactg ctttcactga ggtcaaggat tgtaatattg ccagctttgt aaagccatta 120
aagcagaagt ttcttcagtg atcttctctc taagaaacac catcacctcc atgtgcctta 180
cagaggeece etgegttetg etgeattget tttgegeaat ecettgatga tgaagatggt 240
<210> 380
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 380
acgtacacgc agaccgacat gggnnnttca ggcntnagat caaactcaaa acctgnaatg 60
atatccactc tcttttctt aagctcaggg aaatattcca agtagaagtc canaaagtca 120
teggetaana tgettengaa titgaatica tgeacatagg cettgaaaaa aetgteaaac 180
tgannctgat cacccaccaa gtgggccntn tatgacacaa agcagaaacc tttctcntan 240
g
                                                                   241
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<210> 381

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<211> 241
 <212> DNA
 <213> Homo sapiens
<400> 381
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totaaagaga gggtatttca tatggctttt agttcacttg tttgtatttc atcttgattt 120
ttttctttgg aaaataaagc attctatttg gttcagattt ctcagatttg aaaaaggctc 180
tatctcagat gtagtaaatt atttcctttc agtttgtgaa agcaggattt gactctqaaa 240
<210> 382
<211> 241
<212> DNA
<213> Homo sapiens
<400> 382
gtactgctat aatcaatacg tctgatagac aggtttatcc actatattga ccctacctct 60
aaaaggattg tcataattta tatgctttat gtttacacct atgatacagt tgccttggaa 120
taagaaaatc acaggagtag ataaatactc tagaattcat atacccttgg aagatgggtt 240
                                                                241
<210> 383
<211> 241
<212> DNA
<213> Homo sapiens
<400> 383
ggcaggtaca aagtcttctc tttgcttttt ataattttaa agcaaataac acatttaact 60
gtatttaagt ctgtgcaaat aatccttcag aagaaatatc caagattctg tttgcagagg 120
tcattttgtc tctcaaagat gattaaatga gtttgtcttc agataaagtg ctcctgtcca 180
gcagaactca aaaggccttc aagctgttca gtaagtgtag ttcagataag actccgtcat 240
<210> 384
<211> 241
<212> DNA
<213> Homo sapiens
<400> 384
ggtacacaaa atacacttgc aagcttgctt acagagacct gttaaacaaa gaacagacag 60
attctataaa atcagttata tcaacatata aaggagtgtg attttcagtt tgttttttta 120
agtaaatatg accaaactga ctaaataaga aggcaaaaca aaaaattatg cttccttqac 180
aaggcctttg gagtaaacaa aatgctttaa ggctcctggt gaatggggtt gcaaggatga 240
<210> 385
<211> 241
<212> DNA
<213> Homo sapiens
<400> 385
ggcaggtcta caatggctct gtcccttctg tggaatcgtt acaccaagag gtctcagtcc 60
tggtccctga ccccacagtg agctgtttag atgatccttc acatcttcct gatcaactgg 120
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aagacactcc aatcctcagt gaagactctc tggagccctt caactctctg gcaccaggta 180
ggtttggagg ctatgtccct ttaacttatc catgcagagt agccaaactt tacctgaaag 240
<210> 386
<211> 241
<212> DNA
<213> Homo sapiens
<400> 386
aggtaccttt ttcctctcca aaggaacagt ttctaaagtt ttctgggggg aaaaaaaact 60
tacatcaaat ttaaaccata tgttaaactg catattagtt gtgttacacc aaaaaattgc 120
ctcagctgat ctacacaagt ttcaaagtca ttaatgcttg atataaattt actcaacatt 180
aaattatott aaattattaa ttaaaaaaaa aactttotaa gggaaaaata aacaaatgta 240
<210> 387
<211> 241
<212> DNA
<213> Homo sapiens
<400> 387
accoractgg cogctgtgga gtatctccac totcccctcg tgagggccgc toccaccgac 60
cagtogaact ttogtaaatg gagttaatgt gtttocacto coottttocc ctttotggcc 120
ttttggtcca gaatttcctg gccttccggc atatcctggg agtcctcgac ttccaggaaa 180
gccaattgct ccccgatcac ctttaagacc cggaggacct attggacctg gaaatcttcg 240
<210> 388
<211> 241
<212> DNA
<213> Homo sapiens
<400> 388
tttgtactct tgtccacagc agagacattg agtataccat tggcatcaat gtcaaaagtg 60
acttcaatct gaggaacacc tcggggtgca ggaggtatgc ctgtgagttc aaacttgcca 120
agcaggttgt tatcctttgt catggcacgc tcgccttcat aaacctgaat aagtacacca 180
ggctggttgt cagaataggt agtgaaggtc tgtgtctgct tggtaggaat ggtggtatta 240
<210> 389
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 389
tacctntgtt agtgagcacc ttgtcttntg tgcttatntc ttnaagataa atacatggaa 60
ggatgtgaaa atcggaacac caactatgtg tctcactgca tctaagtgaa gcagccacag 120
ctgtgagagt tttcaaagca gaaagatgct gatgtgacct ctggaattca gacatactga 180
gctatgggtc agaagtgttt tacttaaaaa gcaaacaatc cccaggaaat actgaatagg 240
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241
<210> 390
<211> 241
<212> DNA
<213> Homo sapiens
<400> 390
gcaggtacat ccacatgttc ctccaaatga cgtttggggt cctgcttgcc aacattcttt 60
attgccagct gttcaggtgt catcttatct tcttcttcta cagccttatt gtaattcttg 120
gctaattcca acatctcttt taccactgat tcattgcgtt tacaatgttc actgtagtcc 180
tgaagtgtca aaccttccat ccaactcttc ttatgcaaat ttagcaacat cttctgttcc 240
<210> 391
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 391
cnggcacaan cttntgtttt tnntnttttt ttttttttt tcttttttn tctttattn tttttantnt 60
taaanaaaaa nnntannnaa annngggttt aaatnetntn nncaganeat taaaactgaa 120
ggggaaaaaa aaaccaaaaa cgagcttntt anttnacntg ggnttgggnn gntgctgatn 180
tnaagaagca anntttanan cnngcnnnat ganngagngn tcannttgaa atttnnaccc 240
<210> 392
<211> 241
<212> DNA
<213> Homo sapiens
<400> 392
gaggtactaa atggtatcct tagattaaaa ttttgtgctt gataacagct gtttttcta 60
cattagaaat aagatgccac acaaggaact acattccaga tttaaagaaa tgaaaggata 120
ccattagtgt gtataacaga ttattgttca tacttgtaaa gcatcttatg tcattgagaa 180
tataaagaac agtgccttag aagacagtga aaggtaagct ctagcttaat gtctatgatt 240
<210> 393
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 393
ggcaggtaca taagcataat cagttatgga cagcttcttg tataaattgc tattcancaa 60
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tacataaact qcctnaaaqa tttatgctta caggtagaca ttcaatttac caataaaaca 120
gcatgttctq aaaatatggg cacattttaa aacatattaa gacagttctg ttaaccataa 180
tagtcccaca gtatgactga gtaataagaa tctacttcaa aagnaaaaaa aaaattaatc 240
<210> 394
<211> 241
<212> DNA
<213> Homo sapiens
<400> 394
aggtacagca gcagtagatg gctgcaacaa ccttcctcct accccagccc agaaaatatt 60
tctgccccac cccaggatcc gggaccaaaa taaagagcaa gcaggccccc ttcactgagg 120
tgctgggtag ggctcagtgc cacattactg tgctttgaga aagaggaagg ggatttgttt 180
ggcactttaa aaatagagga gtaagcagga ctggagaggc cagagaagat accaaaattg 240
<210> 395
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 395
nggenggnne caanatatga aatntnanta tnatacatga tnaaaaagett tatntatttt 60
agtgagtaat taagtttaca ctgtgaataa ggattaattc ccagatgacc atctacagtt 120
actaccacat agagggtata cacggatgga tcgattacaa gaatataaaa cttattttcc 180
ttcctgtatc cacatttctt tgcaatgtga atttgcaggc cctctcaaga agtggagtct 240
<210> 396
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 396
gaggtacacc ttgaatgaca atgctnggag cccccctgtg gtcatcgacg cctccactgc 60
cattgatgca ccatccaacc tgcgtttcct ggccaccaca cccaattcct tgctggtatc 120
atggcagccg ccacgtgcca ggattaccgg ctacatcatc aagtatgaga agcctgggtc 180
tecteccaga gaagtggtee eteggeeeeg eeetggtgte acagaggeta etattactgg 240
<210> 397
<211> 241
<212> DNA
<213> Homo sapiens
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<220>
 <221> misc_feature
 <222> (1)...(241)
 <223> n = A,T,C or G
<400> 397
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tcccagaatg tggaaaatat atctgtgcan gatagaaatc ctgcccagag gctgtttctg 120
teteattiga geteteette atgiggeaga getgaetgig geggittagg ageetacatt 180
ttagaaaagc ttacctcaaa gttctgcatt gagcctgagc actggaaagg agataaaata 240
<210> 398
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 398
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contaccent tgcccannac etgaacgege ettntgattg ggacageegt gggaaggaca 120
gttatgaaac nantcanctg gatgaccana gtgntgaaac cnacanncac angenntena 180
cattatataa ncggaaagct aatgatgaga gcaatgatca ttccgatgtn attgatagtc 240
<210> 399
<211> 241
<212> DNA
<213> Homo sapiens
<220> .
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 399
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ctgagcagec cacecettae cetgaegaag geaateetee tetggaatgt etetteeete 120
ttcagtctgg gttctgcctc agccacgaac tgggaaggag tgaggaacat cccaacggca 180
atgagagtat cccagtgact ccaaacagga angaatcagt gttcanaaag tcagggccct 240
<210> 400
<211> 241
`<212> DNA
<213> Homo sapiens
<400> 400
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acaaccatgt gtcttcattt ataacttttt gtttaaaaaa tttttagttc aagtttagtt 120
```

```
cattgatatt atcctctgaa tgcagttaag gctgggcaga aattctactc atgtgacatc 180
tgccacaggt ctattttgaa gcttttcttc taatgggcaa tgtttgtcct taccaggatt 240
<210> 401
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 401
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atgtgtcatc acctgggatt tcatctgggc cgccttttct gggtcaacag ccaacacatg 120
ctggtaatga cggatggtat gtaagcgatc tttgttctca gcacggacat aacgccgtaa 180
ggcctggaga atgcgatgag gccgtggcgg gtcagactgc aaggcagcca ggtagttctc 240
<210> 402
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (241)
<223> n = A,T,C or G
<400> 402
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tagcgaaaaa gtgcaccata attactgctg cactgcagtc atttctgcaa ttcccatgtt 120
tcttaaataa ctatcttgtc agataacaca caatataaag agcaattatg aaaaacagac 180
atttacatat acttctaaag tcttattggg aatatcctgt ttggccattg ggataaccaa 240
<210> 403
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 403
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gccggtcatg tccaaagtaa tggagatgtt ccagcctagt gcggtggtct tacagtgtgg 120
ctcagactcc ctatctgggg atcggttagg ttgcttcaat ctaactatca aaggacacgc 180
caagtgtgtg gaatttgtca agagctttaa cctgcctatg ctgatgctgg gaggcggtgg 240
```

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<210> 404
<211> 241
<212> DNA
<213> Homo sapiens
<400> 404
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ttgtttatag tgagtaacct tgtaggagtc ggtggccagg aggatgttga actcggcttc 180
tgccgcagga ttcatctcgg gccggaggac aaggggcccg cgcgccgcga gctccctgac 240
<210> 405
<211> 266
<212> DNA
<213> Homo sapiens
<400> 405
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aggitticic ccagatitga gaactetaga tictgcatca tiatetitga gictatatic 120
tcttgggctg taagaagatg aggaatgtaa taggtctgcc ccaagccttt catgccttct 180
gtaccaaget tgtttccttg tgcatectte ccaggetetg getgeceett attggagaat 240
gtgatttcca agacaatcaa tccaca
<210> 406
<211> 231
<212> DNA
<213> Homo sapiens
<400> 406
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tcacgcatct cgttcagaat gcggctcagg tccacgccag gtgcagcgtc catctccaca 120
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aggtaggcca gctcctcctt caggctctca atctgcatct ccaggtcagc t
<210> 407
<211> 266
<212> DNA
<213> Homo sapiens
<400> 407
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ttgtgccata atgcagcagt atggagggag gattttatgg agaaatgggg atagtcttca 120
tgaccacaaa taaataaagg aaaactaagc tgcattgtgg gttttgaaaa ggttattata 180
cttcttaaca attcttttt tcagggactt ttctagctgt atgactgtta cttgaccttc 240
tttgaaaagc attcccaaaa tgctct
<210> 408
<211> 261
<212> DNA
<213> Homo sapiens
<400> 408
ctgtgtcagc gagcctcggt acactgattt ccgatcaaaa gaatcatcat ctttaccttg 60
actiticagg gaattactga actitictict cagaagatag ggcacageca tigccitiggc 120
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```
ctcacttgaa gggtctgcat ttgggtcctc tggtctcttg ccaagtttcc cagccactcg 180
 agggagtaat atctggaggg caaagaagag acttatgtta ttgttgaacc tccaqccaca 240
 gggaggagca tgggcatggg t
 <210> 409
 <211> 266
 <212> DNA
 <213> Homo sapiens
 <400> 409
gctgacagta atacactgcc acatcttcag cctgcaggct gctgatggtg agagtgaaat 60
ctgtcccaga cccgctgcca ctgaatcggt cagggatccc ggattcccgg gtagatgccc 120
agtaaatgag cagtttagga ggctgtcctg gtttctgctg gtaccaagct aagtagttct 180
tattgttgga gctgtctaaa acactctggc tggtcttgca gttgatggtg gccctctcgc 240
ccagagacac agccagggag tgtgga
                                                                   .266
<210> 410
<211> 181
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(241)
<223> n = A, T, C or G
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ngntccggtt ccagccaaac cngtngctna ctttccacct tntttccacc tccctcnggt 180
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<400> 411
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gatggcctcc caccattcca agcggagagg ccgggcgtct tctgagagtc agggtctagg 120
tgctggagtg cgcacggagg ccgatgtaga ggaggaggcc ctgaggagga agctggagga 180
gctggccagc aacgtcagtg accaggagac ctcgtccgag gaggaggaag ccaaggacga 240
aaaggcagag cccaacaggg a
<210> 412
<211> 171
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 412
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cagagctgta tctgcaggnt cgtaagcata nagacngttt gaatatcttc cagngatatc 120
ggctctaact gncagagatg ggtcaacaaa cataatcctg gggacatact g
<210> 413
<211> 266
<212> DNA
<213> Homo sapiens
<400> 413
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attittataa agtacigtaa tictticati gaggggctat gigatggaga cagactaact 120
cattttgtta tttgcattaa aattattttg ggtctctgtt caaatgagtt tggagaatgc 180
ttgacttgtt ggtctgtgta aatgtgtata tatatatacc tgaatacagg aacatcggag 240
acctattcac tcccacacac tctgct
                                                                   266
<210> 414
<211> 266
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A,T,C or G
<400> 414
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tocatgacea etcaaggeet ecceancetg ttegteaagt tgteeteaag tecaageaat 120
ggaatccatg tgtttgcaaa aaaagtgtgc tanttttaag gnctttcgta taagaatnaa 180
tganacaatt ttcctaccaa aggangaaca aaaggataaa tataatacaa aatatatgta 240
tatggttgtt tgacaaatta tataac
<210> 415
<211> 266
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C or G
<400> 415
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gtttgcgcaa cgttgttgcc attgctacag gcatcgtggt gtnacgctcg tcgattggta 120
tggcttcatt cagctccggt tcccaacgat caaggcgagt tacatgatcc cccatgttgt 180
gcaaaaaagc ggttagctcc ttcggtcctc cgatcgttgt canaagtaag ttggccgcag 240
tgttatcact catggttatg gcagca
                                                                   266
<210> 416
<211> 878
<212> DNA
<213> Homo sapiens
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ctggaaaaaa totcatacta agcaaacagt agtatotoat accaagcaaa accaagtagt 300
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caaagtcaga treggtgeta accaggtgge atetatgate aacgtegeee etettattta 420
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<210> 417
<211> 514
<212> DNA
<213> Homo sapiens
<400> 417
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aatcaccett geteeteetg ggtgeetgga agatggaetg geagagaeet etttgttgeg 480
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<210> 418
<211> 352
<212> DNA
<213> Homo sapiens
<400> 418
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agtaggetea ggatetgetg aaggteggag gagttagtee eegcaateaa gageetgtet 180
tcctgaagcc cttggtgata ttttgccact cagccaagaa tgaggatgca tccttcagat 240
tetetatgte eegaacetgg aacceateea egecagettg eagecaaaac teeagageat 300
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<210> 419
<211> 344
<212> DNA
<213> Homo sapiens
<400> 419
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attgagactc aaaggcttat actggcgtct gaaactatgt ccttcgttaa acccgtattt 180
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<210> 420
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<212> DNA
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<400> 420
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<212> DNA
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<400> 421
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<212> DNA
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<212> DNA
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taaaatggtc aggttgttgg ggaaaaaaaa gtgccaggct ctctagagaa aaatgtgaag 660
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.125

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agaagcacct gccagcaaca gcttccttct ttgagcttaq tccatccctc atqaaaaatq 780
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<212> DNA
<213> Homo sapiens
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<211> 434
<212> DNA
<213> Homo sapiens
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  cacctgggac agtcatctca aagtcggtgc ctacgaggct gctgagatac tccttgtgcc 360
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  caagtgacca agaccagaag cagggacgat taggctagtt ctgcggcaag gtgaactgga 180
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  <212> DNA
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. tgaaatgact tottaaatat ttagttgata gaotgotaca ggtaataggg.acttagcaag 180
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  <213> Homo sapiens
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 <213> Homo sapiens
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. tccaaaatca tttataaaat gtatttggct ttggaatcca caggacttca aacaagcaaa 180
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 <213> Homo sapiens
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 gtcaccgtct gtcaatgaat attatagaag gtatgaaggt gtaattacca taataacaaa 480
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 <211> 645
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 <213> Homo sapiens
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tgcttcatca agtcagcaag aatagcctgt catatcagtg tatatcaggc tcactcagga 540
taatttccct actgatgagc caaacactaa ctgattttag agcttaacta catctgcaaa 600
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<212> DNA
<213> Homo sapiens
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<212> DNA
<213> Homo sapiens
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aactttatta tccaggacgc tgagagtata acatgcatga cagagctttt agagcactgt 480
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<210> 440
<211> 341
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<212> DNA
 <213> Homo sapiens
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 cagteteact cacaaaaaat aaaateteat gteeceaacg aacceagagt cagacgacag 180
 ctggagcatt ggcagggaca gtcagaaagg agacaagtga aaacggtcag atggacacag 240
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 <211> 572
<212> DNA
<213> Homo sapiens
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<222> (1)...(572)
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ctggccaagg anacttintt titttganaa tattcttcaa aaagctgatc taatgatatg 180
gctctggtcc tacaattcca tgtaacttct aaccttgatt ttatctcatg agcaaatcat 240
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<210> 442
<211> 379
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(379)
<223> n = A,T,C or G
<400> 442
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tcaaggactt gaaagcatcc atgtgtggac tcaagtcctt acctcttccg gagatgtagc 360
aaaacgcatg gagtgtgta
                                                                   379
<210> 443
<211> 511
<212> DNA
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<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(511)
<223> n = A,T,C or G
<400> 443
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ctgttgactt gggcttctag tctctgctcc gtgtctgaca gtgccaagat catgctcccc 240
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gcagacttta caagctgaac caccccagcc atttggctac aagtcttttc taggccatca 360
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ttcaaggcag ctgaaaggac atcnacatct ctgtctctgg tcgggggact acctgcctqt 480
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<210> 444
<211> 612
<212> DNA
<213> Homo sapiens
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<221> misc_feature
<222> (1)...(612)
<223> n = A, T, C or G
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taataaggac caaacaggta ggattcactg acatgacatc atctctgtag ggaaaattag 480
gaggcagttg ccgtatgtat tcctgaatgg agtttggata aataagcaca gtgattgcaa 540
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cgcgttgctt gt
                                                                   612
<210> 445
<211> 708
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(708)
<223> n = A,T,C or G
<400> 445
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caagetggge cagettteat aatggtgtgg etgetggeet gaagataget eetgeeteee 180
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<212> DNA
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gctgtgtttg gaactgctac cgatacatca atggtaggaa ctcctctgat gtcctggttt 300
atgttaccag caatgacact acggtgctgc tacccccgta tgatgatgcc actgtgaatg 360
grgctgccaa ggagccaccg ccaccttacg tgtctgccta agccttcaag tgggcggagc 420
tgagggcagc agcttgactt tgcagacatc tgagcaatag ttctgttatt tcacttttgc 480
catgageete tetgagettg tttgttgetg aaatgetaet ttttaaaatt tagatgttag 540
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<210> 447
<211> 642
<212> DNA
<213> Homo sapiens
<400> 447
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cctttctgat acttttcatt gctaaaataa aacaggcggg aaatgtggaa aagaaattca 120
acaaaataat gtagcaccag aagaacaagt cctagatgat tcaagttcaa aaggtaagct 180
ccagcaatgt ggaagaggta aagaccaatg tagacaagct gacgaggaat atcttctttt 240
ttggttttct ggaagtagag ttcaggaaaa gcatgaagcc agtaagccag ctgtgatatg 300
tagaaaaact tcatttgaaa tgtcatcagg ttatggggat aagccctcca taagatagtt 360
gggtctgaga tgtagttttc agagatgaga atgaatgtgc cccaaacaca ggcaaaaagg 420
attegeetgt taattttate caacatatae tettgaatta eggeatgaat aattategee 540
actagcatgt agaagaaaac agtagccaaa tctttgatgc catagtaata aagggacact 600
gattcagtag cttgttcttc tgttgctggg agggtgacat tg
                                                                642
<210> 448
<211> 394
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(394)
<223> n = A,T,C \text{ or } G
```

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<400> 448
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  caaagngttt gaaaatccag aggttcctag agaggaccag caacagcagc atcagcagcg 120
  tgatgttatc gatgagccca ttattgaaga gccaagccgc ctccaggagt cagtgatgga 180
  ggccagcaga acaaacatag atgagtcagc tatgcctcca ccaccacctc agggagttaa 240
  gcgaaaagct ggacaaattg acccagagcc tgtgatgcct cctcagcagg tagagcagat 300
  ggaaatacca cctgtagagc ttcccccaga agaacctcca aatatctgtc agctaatacc 360
  agagttagaa cttctgccag aaaaagagaa ggag
  <210> 449
  <211> 494
  <212> DNA
  <213> Homo sapiens
  <220>
  <221> misc_feature
  <222> (1)...(494)
  <223> n = A,T,C or G
  <400> 449
  acaaaaaaca caaggaatac aacccaatag aaaatagtcc tgggaatgtg gtcagaagca 60
  aaggentgag tgtetttete aacegtgeaa aageegtgtt etteeeggga aaceaggaaa 120
  aggatccgct actcaaaaac caagaattta aaggagtttc ttaaatttcg accttgtttc 180
  tgaageteae tttteagtge cattgatgtg agatgtgetg gagtggetat taacettttt 240
  ttcctaaaga ttattgttaa atagatattg tggtttgggg aagttgaatt ttttataggt 300
  taaatgtcat tttagagatg gggagaggga ttatactgca ggcagcttca gccatgttgt 360
  gaaactgata aaagcaactt agcaaggctt cttttcatta ttttttatgt ttcacttata 420
  aagtottagg taactagtag gatagaaaca ctgtgtcccg agagtaagga gagaagctac 480
  tattgattag agcc
                                                                     494
  <210> 450
  <211> 547
  <212> DNA
  <213> Homo sapiens
  <400> 450
  actitggget ccagactica etgicettag geatigaaac cateacetgg titgeatiet 60
  tcatgactga ggttaactta aaacaaaaat ggtaggaaag ctttcctatg cttcgggtaa 120
  gagacaaatt tgcttttgta gaattggtgg ctgagaaagg cagacagggc ctgattaaag 180
  aagacatttg tcaccactag ccaccaagtt aagttgtgga acccaaaggt gacggccatg 240
  gaaacgtaga tcatcagctc tgctaagtag ttaggggaag aaacatattc aaaccagtct 300
  ccaaatggga tcctgtggtt acagtgaatg gccactcctg ctttatttt cctgagattg 360
  ccgagaataa catggcactt atactgatgg gcagatgacc agatgaacat catcatccca 420
  agaatatgga accaccgtgc ttgcatcaat agatttttcc ctgttatgta ggcattcctg 480
  ccatccattg gcacttggct cagcacagtt aggccaacaa ggacataata gacaagtcca 540
  aaacagt
                                                                    547
  <210> 451
 <211> 384
 <212> DNA
 <213> Homo sapiens
· <220>
 <221> misc_feature
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```
<222> (1)...(384)
 <223> n = A,T,C or G
 <400> 451
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ctgctggaaa aatccactgg ctcccaagaa aagaaaatgg tctgaagcct ctgttgtggc 120
tctcacaact catctttccc taagtcatca agctccacat cactgaggtc aatgtcatcc 180
tccacgggaa gctcgccatc cctgccgtcc caaggctctc tctcaacgat ggtagggaaa 240
geoecgeete ctacaggtge egtggageea egeocaaaag agageteeet gagaaacteq 300
ttgatgcctt gctcactgaa ggagcctttt agcagagcaa atttcatctt gcgtgcattg 360
atggcggcca tggcggggta ccca
<210> 452
<211> 381
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(381)
<223> n = A,T,C or G
<400> 452
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cctgcagcca gaatctgcaa gcagcgcctg tatgcaacgt ttagggccaa aggctgtctg 120
gtggggttgt tcatcacagc ataatggcct agtaggtcaa ggatccaggg tgtgaggggc 180
tcaaagccag gaaaacgaat cctcaagtcc ttcagtagtc tgatgagaac tttaactgtg 240
gactgagaag cattttcctc gaaccagcgg gcatgtcgga tggctgctaa ngcactctgc 300
aatactttga tatccaaatg gagttctgga tccagttttc naagattggg tggcactgtt 360
gtaatganaa tcttcactgt a
                                                                   381
<210> 453
<211> 455
<212> DNA
<213> Homo sapiens
<400> 453
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caaagaacag gcattcactg cagcctcctg atttgacctg atgggaggga caggagaatg 120
agtcactctg ccaccacttt tcctgccttg gatttgtaga ggatttgttt tgctctaatt 180
tgtttttcct atatctgccc tactaaggta cacagtctgg gcactttgaa aatgttaaag 240
tttttaacgt ttgactgaca gaagcagcac ttaaaggctt catgaatcta ttttccaaaa 300
aaagtatgct ttcagtaaaa cattttacca ttttatctaa ctatgcactg acatttttgt 360
tcttcctgaa aaggggattt atgctaacac tgtattttta atgtaaaaat atacgtgtag 420
agatatttta acttcctgag tgacttatac ctcaa
                                                                   455
<210> 454
<211> 383
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(383)
<223> n = A,T,C or G
```

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<400> 454
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 tacaaaatga attgcggttt tattacatta ataacctttc acctcagggt tttatgaaga 120
 ggaaagggtt ttatgcaaaa gaaagtgcta caattcctaa tcattttaga cactttagga 180
 gggggtgaag tigtatgata aagcagatat titaattati tgttatcitt tigtatigca 240
 agaaatttct tgctagtgaa tcaagaaaac atccagattg acagtctaaa atggctactg 300
 gtattttagt taattcaaaa atgaaacttt tcagtgattc actttactaa cattctattt 360
 gagaaggctt attggtaaag ttt
 <210> 455
 <211> 383
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc_feature
 <222> (1)...(383)
 <223> n = A,T,C or G
 <400> 455
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gtgcaggagc tgacttcttc caaagagttg tggttccggg cagcggtcat tgccgtgccc 120
 attgctggag ggctgatttt agtgttgctt attatgttgg ccctgaggat gcttcgaagt 180
gaaaataaga ggctgcagga tcagcggcaa cagatgctct cccgtttgca ctacagcttt 240
cacggacacc attecaaaaa ggggcaggtt gcaaagttag acttggaatg catggtgccg 300
 gtcagtgggc acgagaactg ctgtctgacc tgtgataaaa tgagacaagc agacctcagc 360
aacgataaga toototogot tgt
                                                                    383
<210> 456
<211> 543
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (543)
<223> n = A,T,C \text{ or } G
<400> 456
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atangtagac tgagtttccg ggcaatgtct gtcctcaaag acatccaaac tgcgttcagg 120
cagctgaaac aggcttcttt cccagtgaca agcatatgtg gtcagtaata caaacgatgg 180
taaatgaggc tactacatag gcccagttaa caaactcctc ttctcctcgg gtaggccatg 240
atacaagtgg aactcatcaa ataatttaaa cccaaggcga taacaacact atttcccatc 300
taaactcatt taagcettéa caatgtegea atggatteag ttaettgeaa acgateeegg 360
gttgtcatac agatacttgt tttttacaca taacgctgtg ccatcccttc cttcactgcc 420
ccagtcaggt ttcctgttgt tggaccgaaa ggggatacat tttagaaatg cttccctcaa 480
gacagaagtg agaaagaaag gagaccctga ggccaggatc tattaaacct ggtgtgtgcg 540
caa
                                                                   543
<210> 457
<211> 544
<212> DNA
<213> Homo sapiens
```

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<220>
 <221> misc_feature
 <222> (1)...(544)
 <223> n = A, T, C or G
<400> 457
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gcccatgtca cattagggac agtgacaaag ccttcccttt tggcagaggg ttggactgag 120
gatagagcaa caatgaaatc attcagttca atgcacagtc cttgcatctg ctcctctqaq 180
aggggatett ggtetettag caaccecage agcetttgta atteateetg tgtttcagaa 240
gtgggctcag ttcccagcct ttcctcctgg actcctttag atggcaaatc ttccatttca 300
ggatttttct tctgctgttc ctgtagcttc attaagactc'tattgactgc acacattgct 360
gcctctcggc acagtgccat gagatcagca ccaacaaagc ctggagttag gtgtgctaag 420
tgacagaaat caaaagcttg aggaagcctc agttttctgc acaatgtttg aagtattctt 480
tecetggatg etteatetgg gatacetagg catatttete ggtegaacet tecegeacqt 540
ctca
<210> 458
<211> 382
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(382)
\langle 223 \rangle n = A,T,C or G
<400> 458
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aaaactggtt gtcctggatg tttgaaaagt tggtcgttgt catggtgtgt tacttcatcc 120
tatctatcat taactccatg gcacaaagtt atgccaaacg aatccagcag cggttgaact 180
cagaggagaa aactaaataa gtagagaaag ttttaaactg cagaaattgg agtggatggg 240
ttctgcctta aattgggagg actccaagcc gggaaggaaa attccctttt ccaacctgta 300
tcaattttta caacttttt cctgaaagca gtttagtcca tactttgcac tgacatactt 360
tttccttctg tgctaaggta ag
                                                                    382
<210> 459
<211> 168
<212> DNA
<213> Homo sapiens
<400> 459
ctcgtactct agccaggcac gaaaccatga agtagcctga tccttcttag ccatcctggc 60
cgccttagcg gtagtaactt tgtgttatga atcacatgaa agcatggaat cttatgaact 120
taatcccttc attaacagga gaaatgcaaa taccttcata tcccctca
<210> 460
<211> 190
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(190)
```

```
<223> n = A,T,C or G
 <400> 460
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 catggatgga gcttcacacg atttcctcct gcggcagcgg cgaaggtcct ctactgctac 120
 acctggcgtc accagtggcc cgtctgcctc aggaactcct ccgagtgagg gaggaggggg 180
 ctcctttccc
 <210> 461
 <211> 495
 <212> DNA
 <213> Homo sapiens
<400> 461
acagacaggc ttctctgcta tcctccaggc agtgtaatag tcaaggaaaa gggcaacagt 60
attggatcat teettagaca etaateaget ggggaaagag tteattggea aaagtgteet 120
cccaagaatg gtttacacca agcagagag acatgtcact gaatggggaa agggaacccc 180
cgtatccaca gtcactgtaa gcatccagta ggcaggaaga tggctttggg cagtggctgg 240
atgaaagcag atttgagata cccagctccg gaacgaggtc atcttctaca ggttcttcct 300
tcactgagac aatgaattca gggtgatcat tctctgaggg gctgagaggt gcttcctcga 360
ttttcactac cacattaget tggetetetg teteagaggg tatetetaag actagggget 420
tggtatatat gtggtcaaaa cgaattagtt cattaatggc ttccagcttg gctgatgacg 480
tccccactga cagag
                                                                   495
<210> 462
<211> 493
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(493)
<223> n = A,T,C or G
<400> 462
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aacagggngt ttacatgatc cctgtaacag ccatggtctc aaactcagat gcttcctcca 120
tctgccaagt gtgttttgga tacagagcac atcgtggctt ctggggtcac actcagctta 180
ggctgtgggt ccacagagca ctcatctggc tgggctatgg tggtggtggc tctactcaag 240
aagcaaagca gttaccagca cattcaaaca gtgtattgaa catctttaa atatcaaagt 300
gagaaacaag aaggcaacat aataatgtta tcagaaagat gttaggaagt aaggacagct 360
gtgtaaagct tgaggctgaa aagtagcttg ccagcttcat ttctttggtt tcttgggtag 420
tgggcgccgg aacagcaaga tgtgaggttc tggttcatgg atcatataat ggacccatcc 480
ctgactctgc tga
<210> 463
<211> 3681
<212> DNA
<213> Homo sapiens
<400> 463
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ctagctggcc ctgtgggcat ttattagtaa agttttaatg acaaaagctt tgagtcaaca 120
cacccgtggg taattaacct ggtcatcccc accctggaga gccatcctgc ccatgggtga 180
tcaaagaagg aacatctgca ggaacacctg atgaggctgc acccttggcg gaaagaacac 240
```

ctgacacage tgaaagettg gtggaaaaaa cacetgatga ggetgeacee ttggtggaaa 300 gaacacctga Cacggctgaa agcttggtgg aaaaaaacacc tgatgaggct gcatccttgg 360 tggagggaac atctgacaaa attcaatgtt tggagaaagc gacatctgga aagttcgaac 420 agtcagcaga agaaacacct agggaaatta cgagtcctgc aaaagaaaca tctgagaaat 480 ttacgtggcc agcaaaagga agacctagga agatcgcatg ggagaaaaaa gaagacacac 540 ctagggaaat tatgagtccc gcaaaagaaa catctgagaa atttacgtgg gcagcaaaag 600 gaagacctag gaagatcgca tgggagaaaa aagaaacacc tgtaaagact ggatgcgtgg 660 caagagtaac atctaataaa actaaagttt tggaaaaagg aagatctaag atgattgcat 720 gtcctacaaa agaatcatct acaaaagcaa gtgccaatga tcagaggttc ccatcagaat 780 ccaaacaaga ggaagatgaa gaatattctt gtgattctcg gagtctcttt gagagttctg 840 caaagattca agtgtgtata cctgagtcta tatatcaaaa agtaatggag ataaatagag 900 aagtagaaga gcctcctaag aagccatctg ccttcaagcc tgccattgaa atgcaaaact 960 ctgttccaaa taaagccttt gaattgaaga atgaacaaac attgagagca gatccgatgt 1020 tcccaccaga atccaaacaa aaggactatg aagaaaattc ttgggattct gagagtctct 1080 gtgagactgt ttcacagaag gatgtgtgtt tacccaaggc tacacatcaa aaaqaaatag 1140 ataaaataaa tggaaaatta gaagagtctc ctaataaaga tggtcttctg aaggctacct 1200 gcggaatgaa agtttctatt ccaactaaag ccttagaatt gaaggacatg caaactttca 1260 aagcagagcc tccggggaag ccatctgcct tcgagcctgc cactgaaatg caaaagtctg 1320 tcccaaataa agccttggaa ttgaaaaatg aacaaacatt gagagcagat gagatactcc 1380 catcagaatc caaacaaaag gactatgaag aaagttcttg ggattctgag agtctctgtg 1440 agactgtttc acagaaggat gtgtgtttac ccaaggctrc rcatcaaaaa gaaatagata 1500 aaataaatgg aaaattagaa gggtctcctg ttaaagatgg tcttctgaag gctaactgcg 1560 gaatgaaagt ttctattcca actaaagcct tagaattgat ggacatgcaa actttcaaag 1620 cagageetee egagaageea tetgeetteg ageetgeeat tgaaatgeaa aagtetgtte 1680 caaataaagc cttggaattg aagaatgaac aaacattgag agcagatgag atactcccat 1740 cagaatccaa acaaaaggac tatgaagaaa gttcttggga ttctgagagt ctctgtgaga 1800 . ctgtttcaca gaaggatgtg tgtttaccca aggctrcrca tcaaaaagaa atagataaaa 1860 taaatggaaa attagaagag totootgata atgatggttt totgaaggot cootgoagaa 1920 tgaaagtttc tattccaact aaagccttag aattgatgga catgcaaact ttcaaagcag 1980 agentecega gaagematet genttegage etgemattga aatgeaaaag tetgttemaa 2040 ataaagcctt ggaattgaag aatgaacaaa cattgagagc agatcagatg ttcccttcag 2100 aatcaaaaca aaagaasgtt gaagaaaatt cttgggattc tgagagtctc cgtgagactg 2160 tttcacagaa ggatgtgtgt gtacccaagg ctacacatca aaaagaaatg gataaaataa 2220 · gtggaaaatt agaagattca actagcctat caaaaatctt ggatacagtt cattcttgtg 2280 aaagagcaag ggaacttcaa aaagatcact gtgaacaacg tacaggaaaa atggaacaaa 2340 tgaaaaagaa gttttgtgta ctgaaaaaga aactgtcaga agcaaaagaa ataaaatcac 2400 agttagagaa ccaaaaagtt aaatgggaac aagagctctg cagtgtgagg tttctcacac 2460 tcatgaaaat gaaaattatc tcttacatga aaattgcatg ttgaaaaagg aaattgccat 2520 gctaaaactg gaaatagcca cactgaaaca ccaataccag gaaaaggaaa ataaatactt 2580 tgaggacatt aagattttaa aagaaaagaa tgctgaactt cagatgaccc taaaactgaa 2640 agaggaatca ttaactaaaa gggcatctca atatagtggg cagcttaaag ttctgatagc 2700 tgagaacaca atgctcactt ctaaattgaa ggaaaaacaa gacaaagaaa tactagaggc 2760 agaaattgaa tcacaccatc ctagactggc ttctgctgta caagaccatg atcaaattgt 2820 gacatcaaga aaaagtcaag aacctgcttt ccacattgca ggagatgctt gtttgcaaag 2880 aaaaatgaat gttgatgtga gtagtacgat atataacaat gaggtgctcc atcaaccact 2940 ttctgaagct caaaggaaat ccaaaagcct aaaaattaat ctcaattatg cmggagatgc 3000 tctaagagaa aatacattgg tttcagaaca tgcacaaaga gaccaacgtg aaacacagtg 3060 tcaaatgaag gaagctgaac acatgtatca aâacgaacaa gataatgtga acaaacacac 3120 tgaacagcag gagtetetag atcagaaatt atttcaacta caaagcaaaa atatgtgget 3180 tcaacagcaa ttagttcatg cacataagaa agctgacaac aaaagcaaga taacaattga 3240 tattcatttt cttgagagga aaatgcaaca tcatctccta aaagagaaaa atgaggagat 3300 atttaattac aataaccatt taaaaaaccg tatatatcaa tatgaaaaag agaaagcaga 3360 aacagaaaac tcatgagaga caagcagtaa gaaacttctt ttggagaaac aacagaccag 3420 atctttactc acaactcatg ctaggaggcc agtcctagca tcaccttatg ttgaaaatct 3480 taccaatagt ctgtgtcaac agaatactta ttttagaaga aaaattcatg atttcttcct 3540

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 <211> 1424
 <212> DNA
 <213> Homo sapiens
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tggagggaac atctgacaaa attcaatgtt tggagaaagc gacatctgga aagttcgaac 420
agtcagcaga agaaacacct agggaaatta cgagtcctgc aaaagaaaca tctgagaaat 480
ttacgtggcc agcaaaagga agacctagga agatcgcatg ggagaaaaaa gaagacacac 540
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gaagacctag gaagatcgca tgggagaaaa aagaaacacc tgtaaagact ggatgcgtgg 660
caagagtaac atctaataaa actaaagttt tggaaaaagg aagatctaag atgattgcat 720
gtcctacaaa agaatcatct acaaaagcaa gtgccaatga tcagaggttc ccatcagaat 780
ccaaacaaga ggaagatgaa gaatattett gtgatteteg gagtetettt gagagttetg 840
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aagtagaaga geeteetaag aageeatetg eetteaagee tgeeattgaa atgeaaaaet 960
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tcccaccaga atccaaacaa aaggactatg aagaaaattc ttgggattct gagagtctct 1080
gtgagactgt ttcacagaag gatgtgtgtt tacccaaggc tacacatcaa aaagaaatag 1140
ataaaataaa tggaaaatta gaaggtaaga accgtttttt atttaaaaat cagttgaccg 1200
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aaatgcaaac catggaaaaa aagagaagtg caatggtcgt aagttgtatg tctcatcagg 1320
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Cys Glu Thr Val Ser Gln Lys Asp Val Cys Leu Pro Lys Ala Thr His 180 185 190

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Thr Phe Lys Ala Glu Pro Pro Glu Lys Pro Ser Ala Phe Glu Pro Ala 165 170 175

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(19) World Intellectual Property Organization International Bureau



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- (21) International Application Number: PCT/US00/05308
- (22) International Filing Date: 15 February 2000 (15.02.2000)
- (25) Filing Language: English
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- (30) Priority Data:

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09/433,826 3 November 1999 (03.11.1999)	US

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- (81) Designated States (national): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.



A3

(54) Title: COMPOSITIONS FOR THE TREATMENT AND DIAGNOSIS OF BREAST CANCER AND METHODS FOR THEIR USE

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as breast cancer, are disclosed. Compositions may comprise one or more breast tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a breast tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as breast cancer. Diagnostic methods based on detecting a breast tumor protein, or mRNA encoding such a protein, in a sample are also provided.

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Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 29-34 48 49 52 53 55-57 are (partially) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1-79 Partially.
Remark on Protest The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: Claims 1-79 partially

Polypeptide (portion) encoded by the polynucleotide sequence SEQ ID NO 2, the encoding polynucleotides, antibodies against the polypeptide and their uses

2. Claims: Inventions 2-464: claims 1-79 partially

(use of) a polypeptide (portion) encoded by the polynucleotide sequence selected from SEQ ID NO 1-175, 178 180 and 182-468, the encoding polynucleotides, or antibodies against the polypeptide as far as applicable

information on patent family members

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